acetylcholine receptor compositions containing the beta 4 subunit; Stephen F. Heinemann, et al., 435/6, **69.1**, 252.3, **320.1**; 536/23.5
[IMAGE AVAILABLE]

14. 5,371,188, Dec. 6, 1994, Neuronal nicotinic acetylcholine receptor compositions; Stephen F. Heinemann, et al., 530/350; 435/6, **69.1**, 252.3, **320.1** [IMAGE AVAILABLE]

15. 5,369,028, Nov. 29, 1994, DNA and mRNA encoding human neuronal nicotinic acetylcholine receptor compositions and cells transformed with same; Michael M. Harpold, et al., 435/252.3, **69.1**, 69.7, 70.1, 71.1, 71.2; 536/23.5, 25.3 [IMAGE AVAILABLE]

16. 5,300,436, Apr. 5, 1994, Genetically modified tyrosine hydroxylase and uses thereof; Menek Goldstein, et al., 435/190, 252.3, **320.1**; 536/23.2 [IMAGE AVAILABLE]

=> s neuron? or microglia?

7840 NEURON?
158 MICROGLIA?
L12 7896 NEURON? OR MICROGLIA?

=> s l12 and neurotox?

1641 NEUROTOX?
L13 869 L12 AND NEUROTOX?

=> s l13 and (cell death or apopto?)

227674 CELL
21859 DEATH
3013 CELL DEATH
(CELL(W)DEATH)
849 APOPTO?
L14 306 L13 AND (CELL DEATH OR APOPTO?)

=> s l14 and method#

1308657 METHOD#
L15 306 L14 AND METHOD#

=> s neurotox?(5a)(inhibit?)

1641 NEUROTOX?
271147 INHIBIT?
L16 128 NEUROTOX?(5A)(INHIBIT?)

=> s l16 and (cell death or apopto?)

227674 CELL
21859 DEATH
3013 CELL DEATH
(CELL(W)DEATH)
849 APOPTO?
L17 49 L16 AND (CELL DEATH OR APOPTO?)

=> d 40-

40. 5,464,871, Nov. 7, 1995, Aromatic nitro and nitroso compounds and their metabolites useful as anti-viral and anti-tumor agents; Ernest Kun, et al., 514/617; 564/166 [IMAGE AVAILABLE]

41. 5,444,042, Aug. 22, 1995, Method of treatment of neurodegeneration with calpain inhibitors; Raymond T. Bartus, et al., 514/2; 435/23, 184; 514/16, 17, 18, 457 [IMAGE AVAILABLE]

42. 5,336,689, Aug. 9, 1994, Tri- and tetra-substituted guanidines and their use as excitatory amino acid antagonists; Eckard Weber, et al., 514/634, 183, 457; 549/288; 552/8; 564/230, 237, 238, 239, 240 [IMAGE AVAILABLE]

43. 5,266,594, Nov. 30, 1993, Inhibitors of nitric oxide synthase and use thereof to prevent glutamate neurotoxicity; Valina L. Dawson, et al., 514/560 [IMAGE AVAILABLE]

44. 5,262,568, Nov. 16, 1993, Tri- and tetra-substituted guanidines and their use as excitatory amino acid antagonists; Eckard Weber, et al., 564/238; 549/288; 552/8; 564/230, 237, 239, 240 [IMAGE AVAILABLE]

45. 5,232,911, Aug. 3, 1993, Mixture of a non-covalent heterodimer complex and a basic amphiphatic peptide as cytotoxic agent; Juan C. Vidal, 514/12; 424/94.3, 542; 514/21; 530/300, 324, 350, 856 [IMAGE AVAILABLE]

46. 5,190,976, Mar. 2, 1993, N,N'-disubstituted guanidines and their use as excitatory amino acid antagonists; Eckard Weber, et al., 514/634 [IMAGE AVAILABLE]

47. 5,093,525, Mar. 3, 1992, N,N'-disubstituted guanidines and their use as excitatory amino acid antagonists; Eckard Weber, et al., 564/238, 239 [IMAGE AVAILABLE]

48. 5,011,834, Apr. 30, 1991, PCP receptor ligands and the use thereof; Eckard Weber, et al., 514/212 [IMAGE AVAILABLE]

49. 4,906,779, Mar. 6, 1990, N,N'-disubstituted guanidines and their use as excitatory amino acid antagonists; Eckard Weber, et al., 564/238 [IMAGE AVAILABLE]

=> s advanced glycation end product

156496 ADVANCED
112 GLYCATION
1559723 END
616123 PRODUCT
L18 1 ADVANCED GLYCATION END PRODUCT

(ADVANCED(W)GLYCATION(W)END(W)PRODUCT)

=> d

1. 5,246,971, Sep. 21, 1993, Method of inhibiting nitric oxide formation; Joseph R. Williamson, et al., 514/634, 866 [IMAGE AVAILABLE]

=> d kwic

US PAT NO: 5,246,971 [IMAGE AVAILABLE] L18: 1 of 1

SUMMARY:

BSUM(10)

In . . . the prevention by methylguanidine of diabetesinduced vascular dysfunction is attributable to its ability to block NO production rather than blocking **advanced** **glycation** **end** **product** formation.

=> e stern, david/in

E#	FILE	FREQUENCY	TERM
E1	USPAT	1	STERN, CHRISTIAN/IN
E2	USPAT	1	STERN, CHRISTOPHER/IN
E3	USPAT	14	--> STERN, DAVID/IN
E4	USPAT	1	STERN, DAVID F/IN
E5	USPAT	27	STERN, DAVID L/IN
E6	USPAT	14	STERN, DAVID M/IN
E7	USPAT	8	STERN, DAVID R/IN
E8	USPAT	1	STERN, DEREK V/IN
E9	USPAT	23	STERN, DONALD J/IN
E10	USPAT	12	STERN, DONALD S/IN
E11	USPAT	1	STERN, DONOVAN P/IN
E12	USPAT	1	STERN, E GEORGE/IN

=> s e3-e7

```
        14 "STERN, DAVID"/IN
         1 "STERN, DAVID F"/IN
        27 "STERN, DAVID L"/IN
        14 "STERN, DAVID M"/IN
         8 "STERN, DAVID R"/IN
L19      64 ("STERN, DAVID"/IN OR "STERN, DAVID F"/IN OR
"STERN, DAVID
L"/
         IN OR "STERN, DAVID M"/IN OR "STERN, DAVID
R"/IN)

=> s l19 and neurotox?

      1641 NEUROTOX?
L20      0 L19 AND NEUROTOX?

=> s l19 and presenilin?

         3 PRESENILIN?
L21      0 L19 AND PRESENILIN?

=> s l19 and (neuron? or microglia?)

      7840 NEURON?
       158 MICROGLIA?
L22      0 L19 AND (NEURON? OR MICROGLIA?)

=> e yan, shi du/in

E#   FILE       FREQUENCY  TERM
--   ----       ---------  ----
E1   USPAT            3    YAN, SAN JYH/IN
E2   USPAT            1    YAN, SAU CHI B/IN
E3   USPAT            0 --> YAN, SHI DU/IN
E4   USPAT            1    YAN, SHIJIA/IN
E5   USPAT            2    YAN, SHIU HANG/IN
E6   USPAT            1    YAN, SUZIE C/IN
E7   USPAT            1    YAN, TAK W/IN
E8   USPAT          117    YAN, TSOUNG Y/IN
E9   USPAT           65    YAN, TSOUNG YUAN/IN
E10  USPAT            1    YAN, TSUN YEE/IN
E11  USPAT            1    YAN, WANG/IN
E12  USPAT            1    YAN, WANG ZHOA/IN

=> e wolozin, benjamin/in

E#   FILE       FREQUENCY  TERM
--   ----       ---------  ----
E1   USPAT            9    WOLOWSKI, ECKARD/IN
E2   USPAT            1    WOLOWYK, MICHAEL W/IN
E3   USPAT            1 --> WOLOZIN, BENJAMIN/IN
E4   USPAT            1    WOLOZIN, BENJAMIN L/IN
E5   USPAT            1    WOLPA, MARK E/IN
E6   USPAT            1    WOLPALKA, KONSTANTIN/IN
E7   USPAT            1    WOLPAW, JONATHAN R/IN
E8   USPAT           12    WOLPE, STEPHEN D/IN
E9   USPAT            2    WOLPENSINGER, WERNER/IN
E10  USPAT            1    WOLPER, ANDRE E/IN
E11  USPAT            1    WOLPER, ANDRE EBERHARD/IN
E12  USPAT            1    WOLPER, DONALD F/IN

=> s e3-e4

         1 "WOLOZIN, BENJAMIN"/IN
         1 "WOLOZIN, BENJAMIN L"/IN
L23      2 ("WOLOZIN, BENJAMIN"/IN OR "WOLOZIN,
BENJAMIN L"/IN)

=> d 1-


1. 5,869,266, Feb. 9, 1999, Human olfactory neuron cultures to
diagnose
Alzheimer's disease; **Benjamin L. Wolozin**, et al., 435/7.21, 325,
368;
436/63, 503, 811 [IMAGE AVAILABLE]

2. 5,811,310, Sep. 22, 1998, The Alz-50 monoclonal antibody and
diagnostic assay for alzheimer's disease; Hossein A. Ghanbari, et al.,
436/518; 435/7.1, 7.21, 7.92, 70.21, 326; 436/528, 531, 811; 530/388.1
[IMAGE AVAILABLE]

=> d 1- ab


US PAT NO:    5,869,266 [IMAGE AVAILABLE]          L23: 1 of
2

ABSTRACT:
The present invention relates to a culture of human olfactory neurons.
The neurons may display a normal neuronal pathology or a pathology
characteristic of a generalized central nervous system disease. The
cultured neurons can be used for neurotoxicity tests, screening for
therapeutic drugs and anti-viral agents, and diagnosing Alzheimer's
disease.

US PAT NO:    5,811,310 [IMAGE AVAILABLE]          L23: 2 of
2

ABSTRACT:
The invention relates to an antigen associated with Alzheimer's
disease
and to antibodies specific for said antigen. This invention further
relates to methods for diagnosing Alzheimer's disease utilizing assays
containing Alzheimer's associated antigen, antibodies specific for said
antigen and samples from an individual suspected of having
Alzheimer's
disease.

=> file epoab

FILE 'EPOABS' ENTERED AT 14:56:06 ON 11 APR 1999

 * EUROPEAN PATENT ABSTRACTS *
 ********************************

=> s l9

L24      0 PRESENILIN?

=> s l18

      9760 ADVANCED
        10 GLYCATION
    348261 END
     71373 PRODUCT
L25      0 ADVANCED GLYCATION END PRODUCT

(ADVANCED(W)GLYCATION(W)END(W)PRODUCT)

=> s l17

       105 NEUROTOX?
     34921 INHIBIT?
         5 NEUROTOX?(5A)(INHIBIT?)
     44761 CELL
       362 DEATH
        75 CELL DEATH
           (CELL(W)DEATH)
        70 APOPTO?
L26      0 L16 AND (CELL DEATH OR APOPTO?)

=> s (neuron? or microglia?) and (neurotox? or neurodegen?)

       831 NEURON?
         2 MICROGLIA?
       105 NEUROTOX?
       228 NEURODEGEN?
L27     68 (NEURON? OR MICROGLIA?) AND (NEUROTOX?
OR NEURODEGEN?)

=> s l27 and screen?

     34918 SCREEN?
L28      6 L27 AND SCREEN?

=> d 1- cit ab


1. US 05449609A, Sep. 12, 1995, Methods for **screening** for
**neurotoxicity** using a clonal human teratocarcinoma cell line;
DONALD
P YOUNKIN, et al., G01N 33/567

US 05449609A                          L28: 1 of 6


ABSTRACT:

Methods for **screening** for excitotoxic effects of an agent on
```

neurons of the central nervous system are provided by the present invention.

2. US 05342942A, Aug. 30, 1994, Pyrazoloquinazolone derivatives as neurotrophic agents; JUAN C JAEN, et al., C07D 487/04; C07D 487/14; C07D
491/147; C07D 495/14

US 05342942A L28: 2 of 6

ABSTRACT:

Pyrazolo[5,1-b]quinazoline compounds, salts thereof, methods of production, intermediates in their production, pharmaceutical compositions containing said compounds, and methods for treating **neurodegenerative** disorders, tumors of **neuronal** origin, inflammation, allergy, and pain, and methods for **screening** compounds
that interact with the neurotrophic receptors using said compositions are
disclosed.

3. US 05334618A, Aug. 2, 1994, Method of preventing NMDA receptor-mediated **neuronal** damage; STUART A LIPTON, A61K 31/13

US 05334618A L28: 3 of 6

ABSTRACT:

Disclosed is a method for reducing non-ischemic NMDA receptor-mediated
neuronal damage in a mammal by administering to the mammal a compound
of the formula shown in FIG. 1 (or a physiologically-acceptable salt thereof), wherein R1 includes an amino group, R2-R17 are independently H
or a short chain aliphatic group comprising 1-5 carbons, and R4 and R10
also may (independently) be a halogen or an acyl group. Also disclosed is
a **screen** for antagonists of NMDA receptor mediated **neurotoxicity**
which have an enhanced prospect for being clinically tolerated and selective against such **neurotoxicity**.

4. WO 09422866A1, Oct. 13, 1994, PYRAZOLOQUINAZOLONE DERIVATIVES AS
NEUROTROPHIC AGENTS; JUAN CARLOS JAEN, et al., C07D 487/04; A61K 31/505

WO 09422866A1 L28: 4 of 6

ABSTRACT:

Pyrazolo[5,1-b] quinazoline compounds, salts thereof, methods of production, intermediates in their production, pharmaceutical compositions containing said compounds, and methods for treating **neurodegenerative** disorders, tumors of **neuronal** origin, inflammation, allergy, and pain, and methods for **screening** compounds
that interact with the neurotrophic receptors using said compositions are
disclosed.

5. WO 09405275A1, Mar. 17, 1994, METHOD OF PREVENTING NMDA
RECEPTOR-MEDIATED **NEURONAL** DAMAGE; STUART A LIPTON, A61K 31/13

WO 09405275A1 L28: 5 of 6

ABSTRACT:

Disclosed is a method for reducing non-ischemic NMDA receptor-mediated
neuronal damage in a mammal by administering to the mammal a compound
of the formula shown in Fig. 1 (or a physiologically-acceptable salt thereof), wherein R1 includes an amino group, R2-R17 are independently H
or a short chain aliphatic group comprising 1-5 carbons, and R4 and R10
also may (independently) be a halogen or an acyl group. Also disclosed is
a **screen** for antagonists of NMDA receptor mediated **neurotoxicity**
which have an enhanced prospect for being clinically tolerated and selective against such **neurotoxicity**.

6. WO 09005138A1, May 17, 1990, CYTOTOXIC AMYLOID PRECURSORS AND
SCREENING ASSAYS USING THEM; RACHAEL L NEVE, et al., C07H 21/04; C12N
5/00; C12N 15/11; C12Q 1/02; G01N 33/48

WO 09005138A1 L28: 6 of 6

ABSTRACT:

Neurotoxic amyloid precursor proteins (NAPP's) are produced, e.g.
using recombinant DNA, and used in an assay to **screen** candidate compounds for their ability to antagonize **neuronal** toxicity. Specifically, **neurons** are cultured in the presence of an NAPP that
has been treated with the candidate compound. The assay is useful to **screen** candidate therapeutics for Alzheimer's Disease. Assays for the presence of NAPP are useful for identifying and monitoring the progression of Alzheimer's Disease.

=> file uspat

FILE 'USPAT' ENTERED AT 15:00:07 ON 11 APR 1999

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 ********************************
 *      WELCOME TO THE          *
 *   U.S. PATENT TEXT FILE      *
 ********************************
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=> s l28

```
      7840 NEURON?
       158 MICROGLIA?
      1641 NEUROTOX?
      1628 NEURODEGEN?
    244698 SCREEN?
L29      815 L27 AND SCREEN?
```

=> s l29 and (peptide or peptidomimetic)

```
     28593 PEPTIDE
       299 PEPTIDOMIMETIC
L30      515 L29 AND (PEPTIDE OR PEPTIDOMIMETIC)
```

=> s l29 and nucleic acid#

```
     22095 NUCLEIC
    469030 ACID#
     21978 NUCLEIC ACID#
           (NUCLEIC(W)ACID#)
L31      393 L29 AND NUCLEIC ACID#
```

=> d 385-

385. 5,212,082, May 18, 1993, Genetically modified tyrosine hydroxylase
and uses thereof; Menek Goldstein, et al., 435/190 [IMAGE AVAILABLE]

386. 5,210,026, May 11, 1993, Human MK gene and method of expression;
Imre Kovesdi, et al., 435/69.1, 252.3, 252.33, 320.1, 488; 536/23.5 [IMAGE AVAILABLE]

387. 5,202,257, Apr. 13, 1993, Isolated **nucleic** **acids** encoding
glutamate receptor protein; Stephen F. Heinemann, et al., 435/252.3, 69.1, 320.1; 536/23.1, 24.3 [IMAGE AVAILABLE]

388. 5,196,333, Mar. 23, 1993, DNA sequences involved in **neuronal**
degeneration, multicellular organisms containing same and uses thereof;

Marin Chalfie, et al., 435/369, 29, 69.1, 70.3; 536/23.5 [IMAGE AVAILABLE]

389. 5,180,820, Jan. 19, 1993, Brain-derived neurotrophic factor; Yves-Alain Barde, et al., 536/23.51; 435/69.1, 69.3, 320.1; 530/399, 412
[IMAGE AVAILABLE]

390. 5,141,856, Aug. 25, 1992, Expression of purified ciliary neurotrophic factor; Franklin D. Collins, et al., 435/69.1, 91.41, 235.1, 252.3, 252.33, 254.2, 254.21, 320.1, 360; 530/350; 536/23.51, 24.31 [IMAGE AVAILABLE]

391. 4,997,929, Mar. 5, 1991, Purified ciliary neurotrophic factor; Franklin D. Collins, et al., 435/365.1, 69.1, 69.4, 320.1, 369; 536/23.5, 23.51 [IMAGE AVAILABLE]

392. 4,866,042, Sep. 12, 1989, Method for the delivery of genetic material across the blood brain barrier; Edward A. Neuwelt, 424/93.2; 514/44 [IMAGE AVAILABLE]

393. 4,666,828, May 19, 1987, Test for Huntington's disease; James F.
Gusella, 435/6, 91.53; 436/811 [IMAGE AVAILABLE]

=> s l30(10a)(compound or composition)

WARNING - PROXIMITY OPERATOR PRECEDENCE
LEVEL CONFLICTS OR IS NOT CONSIS
TENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED
'L30(10A)(COMPOUND'
389711 COMPOUND
455263 COMPOSITION
L32 471 L30(10A)(COMPOUND OR COMPOSITION)

=> s l30(5a)(compound or composition)

WARNING - PROXIMITY OPERATOR PRECEDENCE
LEVEL CONFLICTS OR IS NOT CONSIS
TENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED
'L30(5A)(COMPOUND'
389711 COMPOUND
455263 COMPOSITION
L33 471 L30(5A)(COMPOUND OR COMPOSITION)

=> s l29 and peptidomimetic

299 PEPTIDOMIMETIC
L34 17 L29 AND PEPTIDOMIMETIC

=> d l-

1. 5,892,003, Apr. 6, 1999, Ciliary neurotrophic factor receptor antibodies; Samuel Davis, et al., 530/388.22 [IMAGE AVAILABLE]

2. 5,863,795, Jan. 26, 1999, Nucleic acids that encode peptides which modulate apoptosis; Thomas D. Chittenden, et al., 435/325, 243, 320.1,
410; 536/23.5, 24.31 [IMAGE AVAILABLE]

3. 5,856,171, Jan. 5, 1999, Cell death regulators; Stanley J. Korsmeyer,
435/254.2, 6, 252.3, 810; 530/324, 350, 388.1, 389.1, 827; 536/23.5 [IMAGE AVAILABLE]

4. 5,854,215, Dec. 29, 1998, Modulators of .beta.-amyloid peptide aggregation; Mark A. Findeis, et al., 514/12; 530/324, 345 [IMAGE AVAILABLE]

5. 5,854,204, Dec. 29, 1998, A.beta. peptides that modulate .beta.-amyloid aggregation; Mark A. Findeis, et al., 514/2, 12, 14; 530/324, 326 [IMAGE AVAILABLE]

6. 5,849,897, Dec. 15, 1998, Nucleic acid molecule encoding ciliary neurotrophic factor receptor; Samuel Davis, et al., 536/23.5; 435/69.1, 252.3, 254.2, 320.1, 325, 348; 530/350 [IMAGE AVAILABLE]

7. 5,844,079, Dec. 1, 1998, Vertebrate embryonic pattern-inducing proteins, and uses related thereto; Philip W. Ingham, et al., 530/350; 435/7.1, 69.1, 252.3, 320.1; 530/300; 536/23.1, 23.5 [IMAGE AVAILABLE]

8. 5,834,234, Nov. 10, 1998, Apoptosis associated protein Bbk; Gregory
J. Gallo, 435/69.1, 70.1, 71.1, 243, 375; 530/324, 325, 326, 327, 350 [IMAGE AVAILABLE]

9. 5,817,626, Oct. 6, 1998, Modulators of beta-amyloid peptide aggregation; Mark A. Findeis, et al., 514/12; 530/324, 326, 345 [IMAGE
AVAILABLE]

10. 5,807,708, Sep. 15, 1998, Conservin nucleic acid molecules and compositions; Dean A. Falb, et al., 435/69.1, 252.3, 254.11, 320.1, 325;
536/23.1, 23.5 [IMAGE AVAILABLE]

11. 5,795,734, Aug. 18, 1998, EPH receptor ligands, and uses related thereto; John G. Flanagan, et al., 435/69.1, 7.1, 252.3, 320.1, 325; 530/300, 350; 536/23.1, 23.5 [IMAGE AVAILABLE]

12. 5,767,252, Jun. 16, 1998, **Neuronal** cell growth factor, Narp; Paul Worley, et al., 530/399, 350 [IMAGE AVAILABLE]

13. 5,723,301, Mar. 3, 1998, Method to **screen** compounds that affect
GAPDH binding to polyglutamine; James R. Burke, et al., 435/7.1 [IMAGE
AVAILABLE]

14. 5,700,638, Dec. 23, 1997, Cell death regulator; Stanley J. Korsmeyer, 435/6, 7.1, 7.2, 7.21, 7.31, 7.8, 69.1, 477; 436/501; 530/350
[IMAGE AVAILABLE]

15. 5,656,725, Aug. 12, 1997, Peptides and compositions which modulate
apoptosis; Thomas D. Chittenden, et al., 530/324, 325, 326, 327, 328, 329, 330 [IMAGE AVAILABLE]

16. 5,648,334, Jul. 15, 1997, Methods of treatment using ciliary neurotrophic factor; Samuel Davis, et al., 514/12, 2; 530/350, 399 [IMAGE
AVAILABLE]

17. 5,426,177, Jun. 20, 1995, Ciliary neurotrophic factor receptor; Samuel Davis, et al., 530/395, 350, 839 [IMAGE AVAILABLE]

=> d his

(FILE 'USPAT' ENTERED AT 14:37:16 ON 11 APR 1999)
L1 1583 S 435/4/CCLS
L2 3908 S 435/69.1/CCLS
L3 2 S 435/172.1/CCLS
L4 49 S 435/368/CCLS
L5 5870 S 435/320.1/CCLS
L6 123 S 435/455/CCLS
L7 8933 S L1-L6
L8 1 S L7 AND PRESENILIN?
L9 3 S PRESENILIN?
L10 138 S L7 AND NEUROTOX?
L11 16 S L10 AND PC12
L12 7896 S NEURON? OR MICROGLIA?
L13 869 S L12 AND NEUROTOX?
L14 306 S L13 AND (CELL DEATH OR APOPTO?)
L15 306 S L14 AND METHOD#
L16 128 S NEUROTOX?(5A)(INHIBIT?)
L17 49 S L16 AND (CELL DEATH OR APOPTO?)
L18 1 S ADVANCED GLYCATION END PRODUCT
E STERN, DAVID/IN
L19 64 S E3-E7
L20 0 S L19 AND NEUROTOX?
L21 0 S L19 AND PRESENILIN?
L22 0 S L19 AND (NEURON? OR MICROGLIA?)
E YAN, SHI DU/IN
E WOLOZIN, BENJAMIN/IN
L23 2 S E3-E4

FILE 'EPOABS' ENTERED AT 14:56:06 ON 11 APR 1999
L24 0 S L9
L25 0 S L18
L26 0 S L17
L27 68 S (NEURON? OR MICROGLIA?) AND (NEUROTOX? OR NEURODEGEN?)
L28 6 S L27 AND SCREEN?

FILE 'USPAT' ENTERED AT 15:00:07 ON 11 APR 1999
L29 815 S L28
L30 515 S L29 AND (PEPTIDE OR PEPTIDOMIMETIC)
L31 393 S L29 AND NUCLEIC ACID#
L32 471 S L30(10A)(COMPOUND OR COMPOSITION)
L33 471 S L30(5A)(COMPOUND OR COMPOSITION)
L34 17 S L29 AND PEPTIDOMIMETIC

=> log y

U.S. Patent & Trademark Office LOGOFF AT 15:23:29 ON 11 APR 1999

************** STN Columbus *************
**

FILE 'HOME' ENTERED AT 15:56:10 ON 11 APR 1999

=> medline

MEDLINE IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter "HELP COMMANDS" at an arrow prompt (=>).

=> file medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.15	0.15

FILE 'MEDLINE' ENTERED AT 15:56:17 ON 11 APR 1999

FILE LAST UPDATED: 2 APR 1999 (19990402/UP). FILE COVERS 1966 TO DATE.

MEDLINE has been reloaded to reflect the annual MeSH changes made by
the National Library of Medicine for 1999. Enter HELP RLOAD for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
SUBSTANCE IDENTIFICATION.

=> s presenilin?/ab,bi

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'AB' IS NOT A VALID FIELD CODE
         0 PRESENILIN?/AB
       407 PRESENILIN?/BI
L1     407 PRESENILIN?/AB,BI
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=> s l1 and advanced glycation end product/ab,bi

```
'AB' IS NOT A VALID FIELD CODE
         0 ADVANCED GLYCATION END PRODUCT/AB
     69312 ADVANCED/BI
      1403 GLYCATION/BI
    161501 END/BI
    100849 PRODUCT/BI
        71 ADVANCED GLYCATION END PRODUCT/BI
                ((ADVANCED(W)GLYCATION(W)END(W)PRODUCT)/BI)
L2       0 L1 AND ADVANCED GLYCATION END PRODUCT/AB,BI
```

=> s l1 and rage/ab,bi

```
'AB' IS NOT A VALID FIELD CODE
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       894 RAGE/BI
L3       0 L1 AND RAGE/AB,BI
```

=> s advanced glycation end product/ab,bi

```
'AB' IS NOT A VALID FIELD CODE
         0 ADVANCED GLYCATION END PRODUCT/AB
     69312 ADVANCED/BI
      1403 GLYCATION/BI
    161501 END/BI
    100849 PRODUCT/BI
        71 ADVANCED GLYCATION END PRODUCT/BI
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L4      71 ADVANCED GLYCATION END PRODUCT/AB,BI
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=> s l1 or l4

```
L5     478 L1 OR L4
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=> s l5 and neuron?/ab,bi

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    211506 NEURON?/BI
L6     114 L5 AND NEURON?/AB,BI
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=> s l1 and neuron?/ab,bi

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    211506 NEURON?/BI
L7     111 L1 AND NEURON?/AB,BI
```

=> s l4 and neuron?/ab,bi

```
'AB' IS NOT A VALID FIELD CODE
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    211506 NEURON?/BI
L8       3 L4 AND NEURON?/AB,BI
```

=> d 1- bib ab

YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):y

L8 ANSWER 1 OF 3 MEDLINE
AN 1998405810 MEDLINE
DN 98405810
TI Localization of identified ***advanced*** ***glycation*** ***end*** - ***product*** structures, N epsilon(carboxymethyl)lysine
and pentosidine, in age-related inclusions in human brains.
AU Kimura T; Takamatsu J; Miyata T; Miyakawa T; Horiuchi S
CS Department of Neuropsychiatry, Kumamoto University School of Medicine,
Japan.. tkimura@kaiju.medic.kumamoto-u.ac.jp
SO PATHOLOGY INTERNATIONAL, (1998 Aug) 48 (8) 575-9.
Journal code: BXQ. ISSN: 1320-5463.
CY Australia
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199901
EW 19990104
AB The recent identification of age-related accumulation of advanced glycation end-products (AGE) of the Maillard reaction in ***neurons***
and vessels of the human brain suggests the involvement of AGE in the
aging process. A variety of inclusions such as lipofuscin granules, corpora amylacea, Hirano bodies, granulovacuolar degenerations and
ubiquitin-positive granular structures are found in the aged human brain.
These age-related inclusions contain insoluble and non-degradable proteins. ***Advanced*** ***glycation*** ***end*** - ***product*** -modified proteins are also known to be insoluble and
protease resistant. The similarity between proteins in such inclusions and
AGE-modified proteins suggests the presence of AGE in inclusions. To
investigate this possibility, the presence of two known AGE structures, N
epsilon(carboxymethyl)lysine (CML) and pentosidine, was examined in
age-related inclusions. Immunohistochemical examination of the medial
temporal area of brain tissues obtained at autopsy from seven non-demented
elderly individuals demonstrated positive reactions in lipofuscin granules
and corpora amylacea but not in other inclusions for anti-CML and anti-pentosidine antibodies. As CML and pentosidine are glycoxidation
products among AGE, the results suggest that glycation and/or oxidation
may be involved in the formation of lipofuscin granules and corpora amylacea.

L8 ANSWER 2 OF 3 MEDLINE
AN 1998340856 MEDLINE
DN 98340856
TI Accelerated formation of N epsilon-(carboxymethyl) lysine, an ***advanced*** ***glycation*** ***end*** ***product*** , by
glyoxal and 3-deoxyglucosone in cultured rat sensory ***neurons*** .
AU Niwa H; Takeda A; Wakai M; Miyata T; Yasuda Y; Mitsuma T; Kurokawa K;

Sobue G
CS Department of Neurology, Nagoya University School of Medicine, Japan.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Jul 9) 248 (1) 93-7.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199810
EW 19981002
AB The formation of advanced glycation end products (AGEs) is associated with pathophysiological changes with aging and disease processes. In the neurodegeneration in Alzheimer's disease and other neurodegenerative diseases. AGEs are speculated to play a role in their pathogenesis. We provide the first evidence for the induction of AGEs in cultured ***neuronal*** cells. Glyoxal and 3-deoxyglucosone (3-DG), AGE precursors, induced N epsilon-(carboxymethyl) lysine (CML), a well characterized and major AGE structure, in cultured rat sensory ***neurons*** in a time- and dose-dependent manner. CML formation was prevented by addition of aminoguanidine, an inhibitor of AGE formation. This culture system provides a useful model to analyze the role of the glycoxidation reaction in ***neuronal*** aging and neurodegenerative disorder.

L8 ANSWER 3 OF 3 MEDLINE
AN 96029671 MEDLINE
DN 96029671
TI The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin. Mediation of neurite outgrowth and co-expression of rage and amphoterin in the developing nervous system.
AU Hori O; Brett J; Slattery T; Cao R; Zhang J; Chen J X; Nagashima M; Lundh E R; Vijay S; Nitecki D; et al
CS Department of Physiology, Columbia University, College of Physicians and Surgeons, New York, New York 10032, USA..
NC AG00602 (NIA)
HL21006 (NHLBI)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Oct 27) 270 (43) 25752-61.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199602
AB The receptor for advanced glycation end products (RAGE), a newly-identified member of the immunoglobulin superfamily, mediates interactions of ***advanced*** ***glycation*** ***end*** ***product*** (AGE)-modified proteins with endothelium and other cell types. Survey of normal tissues demonstrated RAGE expression in situations in which accumulation of AGEs would be unexpected, leading to the hypothesis that under physiologic circumstances, RAGE might mediate interaction with ligands distinct from AGEs. Sequential chromatography of bovine lung extract identified polypeptides with M(r) values of approximately 12,000 (p12) and approximately 23,000 (p23) which bound RAGE. NH2-terminal and internal protein sequence data for p23 matched that reported previously for amphoterin. Amphoterin purified from rat brain or recombinant rat amphoterin bound to purified sRAGE in a saturable and dose-dependent manner, blocked by anti-RAGE IgG or a soluble form of RAGE (sRAGE). Cultured embryonic rat ***neurons*** , which express RAGE, displayed dose-dependent binding of 125I-amphoterin which was prevented by blockade of RAGE using antibody to the receptor or excess soluble receptor (sRAGE). A functional correlate of RAGE-amphoterin interaction was inhibition by anti-RAGE F(ab')2 and sRAGE of neurite formation by cortical ***neurons*** specifically on amphoterin-coated substrates. Consistent with a potential role for RAGE-amphoterin interaction in development, amphoterin and RAGE mRNA/antigen were co-localized in developing rat brain. These data indicate that RAGE has physiologically relevant ligands distinct from AGEs which are likely, via their interaction with the receptor, to participate in physiologic processes outside of the context of diabetes and accumulation of AGEs.

=> d his

(FILE 'HOME' ENTERED AT 15:56:10 ON 11 APR 1999)

FILE 'MEDLINE' ENTERED AT 15:56:17 ON 11 APR 1999
L1 407 S PRESENILIN?/AB,BI
L2 0 S L1 AND ADVANCED GLYCATION END PRODUCT/AB,BI
L3 0 S L1 AND RAGE/AB,BI
L4 71 S ADVANCED GLYCATION END PRODUCT/AB,BI
L5 478 S L1 OR L4
L6 114 S L5 AND NEURON?/AB,BI
L7 111 S L1 AND NEURON?/AB,BI
L8 3 S L4 AND NEURON?/AB,BI

=> s (l4)(3a)(receptor#)/ab,bi

'AB' IS NOT A VALID FIELD CODE
0 (RECEPTOR#)/AB
427150 (RECEPTOR#)/BI
L9 4 (L4)(3A)(RECEPTOR#)/AB,BI

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YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):y

L9 ANSWER 1 OF 4 MEDLINE
AN 1999009111 MEDLINE
DN 99009111
TI A redox-triggered ras-effector interaction. Recruitment of phosphatidylinositol 3'-kinase to Ras by redox stress.
AU Deora A A; Win T; Vanhaesebroeck B; Lander H M
CS Department of Biochemistry, Cornell University Medical College, New York, New York 10021, USA.
NC GM55509 (NIGMS)
AI37637 (NIAID)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Nov 6) 273 (45) 29923-8.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199902
EW 19990204
AB Reactive free radical species are known to trigger biochemical events culminating in transcription factor activation and modulation of gene expression. The cytosolic signaling events triggered by free radicals that result in nuclear responses are largely unknown. Here we identify a signaling cascade triggered immediately upon redox activation of Ras. We examined two physiologically relevant models of redox signaling: 1) nitric oxide in human T cells, and 2) advanced glycation end product in rat

pheochromocytoma cells. Reactive free radical species generated by nitric
oxide donors and the interaction of ***advanced*** ***glycation*** ***end*** ***product*** with its ***receptor*** led to the
recruitment of p85/p110 phosphatidylinositol 3'-kinase (PI3K) to the
plasma membrane, where it associated directly with the effector domain of
Ras and became activated. Only the p110beta and p110delta (but not
p110alpha) catalytic subunits were recruited by redox-activated Ras.
Activation of downstream targets of PI3K such as protein kinase B/Akt and
mitogen-activated protein kinase was found to be PI3K dependent. Our study
demonstrates that nitrosative and oxidative stressors trigger
Ras-dependent and PI3K-regulated events in cells and define a biochemical
pathway that is triggered by redox signaling.

L9 ANSWER 2 OF 4 MEDLINE
AN 97368045 MEDLINE
DN 97368045
TI Recombinant ***advanced*** ***glycation*** ***end*** ***product*** ***receptor*** pharmacokinetics in normal and diabetic
rats.
AU Renard C; Chappey O; Wautier M P; Nagashima M; Lundh E; Morser J; Zhao L;
Schmidt A M; Scherrmann J M; Wautier J L
CS Laboratoire de Recherche en Biologie Vasculaire et Cellulaire, Universite
Paris 7, Hopital Lariboisi'ere, France.
SO MOLECULAR PHARMACOLOGY, (1997 Jul) 52 (1) 54-62.
Journal code: NGR. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199710
EW 19971003
AB Vascular dysfunction in patients with diabetes mellitus is related to
advanced glycation end product (AGE) formation. We previously showed that
AGEs produce an increase in vascular permeability and generated an oxidant
stress after binding to the receptor (RAGE) present on endothelium. RAGE,
a 35-kDa protein that belongs to the immunoglobulin superfamily, has been
cloned from a rat lung cDNA library, and recombinant rat soluble RAGE
(rR-RAGE) has been produced in insect cells. The sequence of RAGE is
highly conserved between human and rat. We studied the biological effect
of rR-RAGE and pharmacokinetics of 125I-rR-RAGE after intravenous or
intraperitoneal administration in normal and streptozotocin-induced
diabetic rats. rR-RAGE prevented albumin or inulin transfer through a
bovine aortic endothelial cell monolayer, restored the hyperpermeability
observed in diabetic rats or induced in normal rats by diabetic rat red
blood cells, and corrected the reactive oxygen intermediate production
after intravenous or intraperitoneal administration. After intravenous
injection of 125I-rR-RAGE, the distribution half-life was longer (p < or =
0.01) in diabetic (0.15 and 4.01 hr) than in normal (0.02 and 0.21 hr)
rats, as was the case for the elimination half-lives (diabetic, 57.17 hr;
normal, 26.02 hr; p < or = 0.01). Distribution volume was higher in
diabetic than in normal rats (6.94 and 3.24 liter/kg, respectively; p =
0.049). Our study showed that rR-RAGE was biologically active in vivo and
slowly cleared, which suggests it could be considered as a potential
therapy.

L9 ANSWER 3 OF 4 MEDLINE
AN 96289840 MEDLINE
DN 96289840
TI Recent progress in advanced glycation and diabetic vascular disease: role
of ***advanced*** ***glycation*** ***end*** ***product*** ***receptors*** .
AU Vlassara H; Bucala R
CS Picower Institute for Medical Research, Manhasset, New York 10030, USA.
SO DIABETES, (1996 Jul) 45 Suppl 3 S65-6. Ref: 17
Journal code: E8X. ISSN: 0012-1797.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199610
AB Advanced glycosylation end products (AGEs) form principally from the
rearrangement of early glycation products, i.e., Amadori products, which
produce a class of stable moieties that possess distinctive chemical
crosslinking and biological properties. It has been generally believed
that proteins with half-lives of longer than a few weeks are most
susceptible to advanced glycosylation and that the highest levels of AGEs
occur on proteins that comprise the long-lived structural components of
connective tissue matrix and basement membrane.

L9 ANSWER 4 OF 4 MEDLINE
AN 95096076 MEDLINE
DN 95096076
TI Receptor-mediated endocytic uptake of methylglyoxal-modified serum
albumin. Competition with advanced glycation end product-modified serum
albumin at the ***advanced*** ***glycation*** ***end*** ***product*** ***receptor*** .
AU Westwood M E; McLellan A C; Thornalley P J
CS Department of Chemistry and Biological Chemistry, University of Essex,
Colchester, United Kingdom.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Dec 23) 269 (51) 32293-8.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199503
AB Methylglyoxal binds and irreversibly modifies arginine and lysine residues
in bovine serum albumin (BSA) under physiological conditions, producing a
protein with an increased net negative charge at physiological pH. At 4
degrees C, methylglyoxal-modified BSA (MG-BSA) was bound by cell surface
receptors on murine P388D1 macrophages. The apparent dissociation constant
KD value was 435 +/- 2 nM, and there were 8.89 +/- 0.02 x 10(5)
receptors/cell (n = 6), compare with an apparent KD value of 263 +/- 52 nM
and 10.17 +/- 0.93 x 10(5) receptors/cell (n = 11) for advanced glycation
end product-modified BSA (AGE-BSA). AGE-BSA competed with MG-BSA for
binding to a common receptor; however, a component of AGE-BSA receptor
binding could not be displaced by MG-BSA, and a component of MG-BSA
receptor binding could not be displaced by AGE-BSA, suggesting that there
are binding sites for both AGE-BSA and MG-BSA, competitive and
noncompetitive, to MG-BSA and AGE-BSA on P388D1 cells at 4 degrees C. At
37 degrees C, receptor binding of AGE-BSA and MG-BSA was

followed by
endocytosis and lysosomal degradation of the modified protein.
Methylglyoxal-modified proteins are ligands for the AGE receptor, and
their formation and metabolism may be linked to the development of
diabetic complications.

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2 FILES SEARCHED...
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'AB' IS NOT A VALID FIELD CODE
4 FILES SEARCHED...
L10 0 L1 AND L9

=> s mutant presenilin-2/ab,bi

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L11 10 MUTANT PRESENILIN-2/AB,BI

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PROCESSING COMPLETED FOR L11
L12 4 DUP REM L11 (6 DUPLICATES REMOVED)

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YOU HAVE REQUESTED DATA FROM 4 ANSWERS -
CONTINUE? Y/(N):y

L12 ANSWER 1 OF 4 MEDLINE DUPLICATE 1
AN 1998361992 MEDLINE
DN 98361992
TI Molecular dissection of domains in ***mutant*** ***presenilin***
2 that mediate overproduction of amyloidogenic forms of amyloid
beta peptides. Inability of truncated forms of PS2 with familial
Alzheimer's disease mutation to increase secretion of Abeta42.
AU Tomita T; Tokuhiro S; Hashimoto T; Aiba K; Saido T C; Maruyama K; Iwatsubo
T
CS Department of Neuropathology and Neuroscience, Graduate School of
Pharmaceutical Sciences, University of Tokyo, Tokyo 113-0033, Japan.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Aug 14) 273 (33) 21153-60.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199811
EW 19981103
AB Mutations in presenilin (PS) 1 or PS2 genes account for the majority of
early-onset familial Alzheimer's disease, and these mutations have been
shown to increase production of species of amyloid beta peptide (Abeta)
ending at residue 42, i.e. the most amyloidogenic form of Abeta. To gain
insight into the molecular mechanisms whereby mutant PS induces
overproduction of Abeta42, we constructed cDNAs encoding mutant and/or
truncated forms of PS2 and examined the secretion of Abeta42 from COS or
neuro2a cells transfected with these genes. Cells expressing full-length
PS2 harboring both N141I and M239V mutations in the same polypeptide
induced overproduction of Abeta42, although the levels of Abeta42 were
comparable with those in cells engineered to express PS2 with one or the
other of these PS2 mutations. In contrast, cells engineered to express
partially truncated PS2 (eliminating the COOH-terminal third of PS2 while
retaining the endoproteolytic NH2-terminal fragment) and harboring a N141I
mutation, as well as cells expressing COOH-terminal fragments of PS2, did
not overproduce Abeta42, and the levels of Abeta42 were comparable with
those in cells that expressed full-length, wild-type PS2 or fragments
thereof. These data indicate that: (i) the Abeta42-promoting effects of
mutant PS2 proteins reach the maximum level with a given single amino acid
substitution (i.e. N141I or M239V); and (ii) the expression of full-length
mutant PS2 is required for the overproduction of Abeta42. Hence,
cooperative interactions of NH2- and COOH-terminal fragments generated
from full-length mutant PS2 may be important for the overproduction of
Abeta42 that may underlie familial Alzheimer's disease.

L12 ANSWER 2 OF 4 MEDLINE DUPLICATE 2
AN 1998311214 MEDLINE
DN 98311214
TI ***Mutant*** ***presenilin*** ***2*** transgenic mouse: effect
on an age-dependent increase of amyloid beta-protein 42 in the brain.
AU Oyama F; Sawamura N; Kobayashi K; Morishima-Kawashima M; Kuramochi T; Ito
M; Tomita T; Maruyama K; Saido T C; Iwatsubo T; Capell A; Walter J;
Grunberg J; Ueyama Y; Haass C; Ihara Y
CS Department of Neuropathology, Faculty of Medicine, University of Tokyo,
Japan.
SO JOURNAL OF NEUROCHEMISTRY, (1998 Jul) 71 (1) 313-22.
Journal code: JAV. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199809
EW 19980902
AB The N141I missense mutation in presenilin (PS) 2 is tightly linked with a
form of autosomal dominant familial Alzheimer's disease (AD) in the Volga
German families. We have generated transgenic mouse lines overexpressing
human wild-type or mutant PS2 under transcriptional control of the chicken
beta-actin promoter. In the brains of transgenic mice, the levels of human
PS2 mRNA were found to be five- to 15-fold higher than that of endogenous
mouse PS2 mRNA. The amyloid beta-protein (Abeta) 42 levels in the brains
of mutant PS2 transgenic mice were higher than those in wild-type PS2
transgenic mice at the age of 2, 5, or 8 months. In addition, the

Abeta42
levels appeared to increase steadily in the mutant PS2 transgenic mouse
brains from 2 to 8 months of age, whereas there was only a small increase
in wild-type transgenic mice between the ages of 5 and 8 months. There was
no definite difference in the levels of N-terminal and C-terminal
fragments between wild-type and mutant PS2 transgenic mice at the age of
2, 5, or 8 months. These data show a definite effect of the PS2 mutation
on an age-dependent increase of Abeta42 content in the brain.

L12 ANSWER 3 OF 4 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1999:32127 BIOSIS
DN PREV199900032127
TI Molecular dissection of domains in ***mutant*** ***presenilin***
2 that mediate overproduction of Abeta42.
AU Iwatsubo, T. (1); Tomita, T. (1); Tokuhiro, S. (1); Hashimoto, T. (1);
Koyama, A. (1); Takasugi, N. (1); Aiba, K. (1); Saido, T. C.; Maruyama, K.
CS (1) Dep. Neuropathol. Neurosci., Univ. Tokyo, Tokyo Japan
SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 6.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1
Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience
. ISSN: 0190-5295.
DT Conference
LA English

L12 ANSWER 4 OF 4 CAPLUS COPYRIGHT 1999 ACS
AN 1997:173947 CAPLUS
DN 126:275853
TI The presenilin 2 mutation (N141I) linked to familial Alzheimer disease
(Volga German families) increases the secretion of amyloid .beta. protein
ending at the 42nd (or 43rd) residue
AU Tomita, Taisuke; Maruyama, Kei; Saido, Takaomi C.; Kume, Hideaki;
Shinozaki, Kohki; Tokuhiro, Shinya; Capell, Anja; Walter, Jochen;
Grunberg, Jurgen; Haass, Christian; Iwatsubo, Takeshi; Obata, Kunihiko
CS Lab. Neurochemistry, Natl. Inst. Physiol. Sci., Okazaki, 444, Japan
SO Proc. Natl. Acad. Sci. U. S. A. (1997), 94(5), 2025-2030
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB To gain insights into the significance of presenilins (PS) in the
pathogenetic mechanisms of early-onset familial Alzheimer disease (FAD),
the authors expressed cDNAs for wild-type PS2 and PS2 with the Volga
German (N141I) mutation in cultured cells and then examd. the metab. of
the transfected proteins and their effect on the C-terminal properties of
secreted amyloid .beta. protein (A.beta.). PS2 was identified as a
50-55-kDa protein, which was cleaved to produce N-terminal fragments of
35-40 kDa and C-terminal fragments of 19-23 kDa. The Volga German (N141I)
mutation did not cause any significant change in the metab. of PS2. COS-1
cells doubly transfected with cDNAs for N141I mutant PS2 and human
.beta.-amyloid precursor protein (.beta.APP) or a C-terminal fragment
thereof, as well as mouse Neuro2a neuroblastoma cells stably transfected
with N141I mutant PS2 alone, secreted 1.5-10-fold more A.beta. ending at
residues 42 (or 43) [A.beta.42(43)] compared with those expressing the
wild-type PS2. Apparently, the PS2 mutation (N141I) linked to FAD alters
the metab. of A.beta./.beta.APP to foster the prodn. of the form of
A.beta. that most readily deposits in amyloid plaques. Thus, mutant PS2
may lead to AD by altering the metab. of A.beta./.beta.APP.

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E1 1 STERN DARRYL/AU
E2 4 STERN DARRYL A/AU
E3 162 --> STERN DAVID/AU
E4 9 STERN DAVID A/AU
E5 84 STERN DAVID B/AU
E6 1 STERN DAVID BENJAMIN/AU
E7 2 STERN DAVID E/AU
E8 71 STERN DAVID F/AU
E9 1 STERN DAVID FREDERICK/AU
E10 2 STERN DAVID H/AU
E11 4 STERN DAVID I/AU
E12 40 STERN DAVID L/AU

=> s e3

L13 162 "STERN DAVID"/AU

=> s l13 and presenilin?/ab,bi

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L14 0 L13 AND PRESENILIN?/AB,BI

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E1 1 YAN SHENTSHAN/AU
E2 7 YAN SHI/AU
E3 73 --> YAN SHI DU/AU
E4 28 YAN SHI FANG/AU
E5 1 YAN SHI G/AU
E6 1 YAN SHI KUN/AU
E7 1 YAN SHI LEI/AU
E8 1 YAN SHI MING/AU
E9 1 YAN SHI PIN/AU
E10 45 YAN SHI PING/AU
E11 1 YAN SHI QI/AU
E12 2 YAN SHI QIANG/AU

=> s e2-e3

L15 80 ("YAN SHI"/AU OR "YAN SHI DU"/AU)

=> s l15 and presenilin?/ab,bi

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L16 0 L15 AND PRESENILIN?/AB,BI

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E1 3 WOLOZIN M W/AU
E2 2 WOLOZIN R/AU
E3 0 --> WOLOZIN, BENJAMIN/AU
E4 1 WOLOZON B L/AU
E5 1 WOLOZSZUK R/AU
E6 1 WOLOZYN W/AU
E7 2 WOLPA BRENDA/AU
E8 1 WOLPA LORI J/AU
E9 3 WOLPA M E/AU
E10 1 WOLPART S I/AU
E11 6 WOLPAW D R/AU
E12 2 WOLPAW DANIEL R/AU

=> e wolozin, b/au

E1 3 WOLOZIN M W/AU
E2 2 WOLOZIN R/AU
E3 0 --> WOLOZIN, B/AU
E4 1 WOLOZON B L/AU
E5 1 WOLOZSZUK R/AU
E6 1 WOLOZYN W/AU
E7 2 WOLPA BRENDA/AU
E8 1 WOLPA LORI J/AU
E9 3 WOLPA M E/AU
E10 1 WOLPART S I/AU
E11 6 WOLPAW D R/AU
E12 2 WOLPAW DANIEL R/AU

=> e wolozin b/au

E1 1 WOLOZEN J J JR/AU
E2 1 WOLOZIA B/AU
E3 84 --> WOLOZIN B/AU
E4 1 WOLOZIN B I/AU
E5 1 WOLOZIN B J/AU
E6 70 WOLOZIN B L/AU
E7 3 WOLOZIN BEN/AU
E8 1 WOLOZIN BENJAMEN L/AU
E9 25 WOLOZIN BENJAMIN/AU
E10 16 WOLOZIN BENJAMIN L/AU
E11 3 WOLOZIN M W/AU
E12 2 WOLOZIN R/AU

=> s e3-e10

L17 201 ("WOLOZIN B"/AU OR "WOLOZIN B I"/AU OR "WOLOZIN B J"/AU OR "WOLO
ZIN B L"/AU OR "WOLOZIN BEN"/AU OR "WOLOZIN BENJAMEN L"/AU OR
"WOLOZIN BENJAMIN"/AU OR "WOLOZIN BENJAMIN L"/AU)

=> s l17 and presenilin/ab,bi

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'AB' IS NOT A VALID FIELD CODE
L18 23 L17 AND PRESENILIN/AB,BI

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PROCESSING COMPLETED FOR L18
L19 12 DUP REM L18 (11 DUPLICATES REMOVED)

=> d 1- bib ab

YOU HAVE REQUESTED DATA FROM 12 ANSWERS - CONTINUE? Y/(N):y

L19 ANSWER 1 OF 12 CAPLUS COPYRIGHT 1999 ACS
AN 1998:258266 CAPLUS
DN 129:52570
TI Regulation of apoptosis by ***presenilin*** 1
AU ***Wolozin, B.*** ; Alexander, P.; Palacino, J.
CS Department of Pharmacology, Loyola University Medical Center, Maywood, IL, 60153, USA
SO Neurobiol. Aging (1998), 19(Suppl. 1, Proceedings of the 11th Annual Tokyo Institute of Psychiatry International Symposium, 1997), S23-S27
CODEN: NEAGDO; ISSN: 0197-4580
PB Elsevier Science Inc.
DT Journal
LA English
AB Familial Alzheimer's disease is transmitted as an autosomal dominant disorder and, in 5-10% of the cases, is caused by mutations in the coding regions of two homologous genes. ***Presenilin*** 1 and 2 (PS1 and PS2). Previously, we have shown that PS2, a homolog of PS1, regulates apoptosis induced in neurons by trophic withdrawal or A.beta., and in T-cells by Fas ligand. We now report that PS1 also regulates apoptosis. Both wild-type and the H115Y mutant form of PS1 enhance Fas-mediated apoptosis in Jurkat cells. We also obsd. that wild-type and the H115Y mutant form of PS1 differentially regulate Jun Kinase, an important enzyme regulating apoptosis.

L19 ANSWER 2 OF 12 MEDLINE DUPLICATE 1
AN 1998356210 MEDLINE
DN 98356210
TI ***Presenilin*** 1 associates with glycogen synthase kinase-3beta and its substrate tau.
AU Takashima A; Murayama M; Murayama O; Kohno T; Honda T; Yasutake K; Nihonmatsu N; Mercken M; Yamaguchi H; Sugihara S; ***Wolozin B***
CS Laboratory for Alzheimer's Disease, Brain Science Institute, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 350-01, Japan.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Aug 4) 95 (16) 9637-41.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199811
EW 19981102
AB Families bearing mutations in the ***presenilin*** 1 (PS1) gene develop Alzheimer's disease. Previous studies have shown that the Alzheimer-associated mutations in PS1 increase production of amyloid beta protein (Abeta1-42). We now show that PS1 also regulates phosphorylation of the microtubule-associated protein tau. PS1 directly binds tau and a tau kinase, glycogen synthase kinase 3beta (GSK-3beta). Deletion studies show that both tau and GSK-3beta bind to the same region of PS1, residues 250-298, whereas the binding domain on tau is the microtubule-binding repeat region. The ability of PS1 to bring tau and GSK-3beta into close proximity suggests that PS1 may regulate the interaction of tau with GSK-3beta. Mutations in PS1 that cause Alzheimer's disease increase the ability of PS1 to bind GSK-3beta and, correspondingly, increase its tau-directed kinase activity. We propose that the increased association of GSK-3beta with mutant PS1 leads to increased phosphorylation of tau.

L19 ANSWER 3 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1999:67066 BIOSIS
DN PREV199900067066
TI Association of ***presenilin*** 1 with beta-catenin.
AU Takashima, A. (1); Murayama, M. (1); Murayama, O. (1); Honda, T. (1); Palacino, James; ***Wolozin, Benjamin***
CS (1) Lab. Alzheimer's Dis., RIKEN, BSI, 2-1 Hirosawa, Wako-shi, Saitama 350-01 Japan
SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 758.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1 Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience . ISSN: 0190-5295.
DT Conference
LA English

L19 ANSWER 4 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1999:48375 BIOSIS
DN PREV199900048375
TI ***Presenilin*** 1 regulates stimulated cleavage of the amyloid precursor protien.
AU Palacino, J. J. (1); Berechid, B.; Alexander, P. (1); Nye, J.; ***Wolozin, B. (1)***
CS (1) Dep. Pharmacol., Loyola Univ. Chicago, Maywood, IL 60153 USA
SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 470.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1 Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience . ISSN: 0190-5295.
DT Conference
LA English

L19 ANSWER 5 OF 12 MEDLINE DUPLICATE 2
AN 1998409316 MEDLINE

DN 98409316
TI Direct association of ***presenilin*** -1 with beta-catenin.
AU Murayama M; Tanaka S; Palacino J; Murayama O; Honda T; Sun X; Yasutake K;
Nihonmatsu N; ***Wolozin B*** ; Takashima A
CS Laboratory for Alzheimer's Disease, Brain Science Institute, RIKEN,
Saitama, Japan.
SO FEBS LETTERS, (1998 Aug 14) 433 (1-2) 73-7.
Journal code: EUH. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199812
EW 19981201
AB Families bearing mutations in the ***presenilin*** -1 (PSI) gene
develop Alzheimer's disease (AD). However, the mechanism through which PS1
causes AD is unclear. The co-immunoprecipitation with PS1 in transfected
COS-7 cells indicates that PSI directly interacts with endogenous
beta-catenin, and the interaction requires residues 322450 of PSI and
445-676 of beta-catenin. Both proteins are co-localized in the endoplasmic
reticulum. Over-expression of PS1 reduces the level of cytoplasmic
beta-catenin, and inhibits beta-catenin-T cell factor-regulated
transcription. These results indicate that PSI plays a role as inhibitor
of the beta-catenin signal, which may be connected with the AD
dysfunction.

L19 ANSWER 6 OF 12 MEDLINE DUPLICATE 3
AN 1998220955 MEDLINE
DN 98220955
TI Regulation of apoptosis by ***presenilin*** 1.
AU ***Wolozin B*** ; Alexander P; Palacino J
CS Department of Pharmacology, Loyola University Medical Center, Maywood, IL
60153, USA.. bwolozi@wpo.it.luc.edu
SO NEUROBIOLOGY OF AGING, (1998 Jan-Feb) 19 (1 Suppl) S23-7.
Journal code: NX5. ISSN: 0197-4580.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199808
EW 19980803
AB Familial Alzheimer's disease is transmitted as an autosomal dominant
disorder and, in 5-10% of the cases, is caused by mutations in the coding
regions of two homologous genes, ***Presenilin*** 1 and 2 (PS1 and
PS2). Previously, we have shown that PS2, a homolog of PS1. regulates
apoptosis induced in neurons by trophic withdrawal or Abeta, and in
T-cells by Fas ligand. We now report that PS1 also regulates apoptosis.
Both wild-type and the H115Y mutant form of PS1 enhance Fas-mediated
apoptosis in Jurkat cells. We also observed that wild-type and the H115Y
mutant form of PS1 differentially regulate Jun Kinase, an important enzyme
regulating apoptosis.

L19 ANSWER 7 OF 12 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998132311 EMBASE
TI Regulation of apoptosis by ***presenilin*** 1.
AU ***Wolozin B.*** ; Alexander P.; Palacino J.
CS B. Wolozin, Department of Pharmacology, Loyola University Medical Center,
Building 102, 2160 South First Avenue, Maywood, IL 60153, United States.
bwolozi@wpo.it.luc.edu
SO Neurobiology of Aging, (1998) 19/SUPPL. 1 (S23-S27).
Refs: 27
ISSN: 0197-4580 CODEN: NEAGDO
PUI S0197458098000414
CY United States
DT Journal; Conference Article
FS 008 Neurology and Neurosurgery
020 Gerontology and Geriatrics
021 Developmental Biology and Teratology
022 Human Genetics
032 Psychiatry
LA English
SL English
AB Familial Alzheimer's disease is transmitted as an autosomal dominant
disorder and, in 5-10% of the cases, is caused by mutations in the coding
regions of two homologous genes. ***Presenilin*** 1 and 2 (PS1 and
PS2). Previously, we have shown that PS2, a homolog of PS1, regulates
apoptosis induced in neurons by trophic withdrawal or A.beta., and in
T-cells by Fas ligand. We now report that PS1 also regulates apoptosis.
Both wild-type and the H115Y mutant form of PS1 enhance Fas-mediated
apoptosis in Jurkat cells. We also observed that wild-type and the H115Y
mutant form of PS1 differentially regulate Jun Kinase, an important enzyme
regulating apoptosis.

L19 ANSWER 8 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:527282 BIOSIS
DN PREV199799826485
TI Mutant PS1 stimulates the JNK signal transduction cascade.
AU Palacino, J. J.; Alexander, P.; St.george-Hyslop, P.; Takashima, A.;
Schultz, R.; ***Wolozin, B.***
CS Dep. Pharmacol., Loyola Univ. Chicago Med. Cent., Maywood, IL 60153 USA
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 1117.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience New
Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

L19 ANSWER 9 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:527284 BIOSIS
DN PREV199799826487
TI ***Presenilin*** -2 couples with the signal transduction system of the
RAGE receptor.
AU ***Wolozin, B.*** ; Alexander, P.; Stern, D.; Schmidt, A. M.; Yan, S.
D.
CS Dep. Pharmacol., Loyola Univ. Chicago Med. Cent., Maywood, IL 60153 USA
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 1117.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience New
Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

L19 ANSWER 10 OF 12 MEDLINE DUPLICATE 4
AN 97094860 MEDLINE
DN 97094860
TI Requirement of the familial Alzheimer's disease gene PS2 for apoptosis.
Opposing effect of ALG-3.
AU Vito P; ***Wolozin B*** ; Ganjei J K; Iwasaki K; Lacana E; D'Adamio L
CS T-Cell Molecular Biology Unit, Laboratory of Cellular and Molecular
Immunology, NIAID, National Institutes of Health, Maryland 20892, USA..
ldadamio@atlas.niaid.nih.gov
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Dec 6) 271 (49) 31025-8.
Journal code: HIV. ISSN: 0021-9258.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-U49111; GENBANK-U57324; GENBANK-U57325
EM 199703
AB ALG-3, a truncated mouse homologue of the chromosome 1 familial
Alzheimer's disease gene PS2, rescues T hybridoma 3DO cells from T-cell
receptor-induced apoptosis by inhibiting Fas ligand induction and Fas
signaling. Here we show that ALG-3 transfected 3DO cells express a
COOH-terminal PS2 polypeptide. Overexpression of PS2 in ALG-3 transfected
3DO cells reconstitutes sensitivity to receptor-induced cell death,
suggesting that the artificial PS2 polypeptide functions as a dominant
negative mutant of PS2. ALG-3 and antisense PS2 protect PC12 cells from
glutamate-induced apoptosis but not from death induced by hydrogen
peroxide or the free radical MPP+. Thus, the PS2 gene is required for some
forms of cell death in diverse cell types, and its function is opposed by
ALG-3.

L19 ANSWER 11 OF 12 MEDLINE DUPLICATE 5
AN 97094374 MEDLINE
DN 97094374
TI Participation of ***presenilin*** 2 in apoptosis: enhanced basal
activity conferred by an Alzheimer mutation.
AU ***Wolozin B*** ; Iwasaki K; Vito P; Ganjei J K; Lacan'a E; Sunderland
T; Zhao B; Kusiak J W; Wasco W; D'Adamio L
CS Unit on Alzheimer Biology, Laboratory of Clinical Science, National
Institute of Mental Health, Building 10, Room 3D41, 9000 Rockville Pike,
Bethesda, MD 20892, USA.. ldadamio@atlas.niaid.nih.gov
SO SCIENCE, (1996 Dec 6) 274 (5293) 1710-3.
Journal code: UJ7. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199703
AB Overexpression of the familial Alzheimer's disease gene ***Presenilin***
2 (PS2) in nerve growth factor-differentiated PC12 cells increased
apoptosis induced by trophic factor withdrawal or beta-amyloid.
Transfection of antisense PS2 conferred protection against apoptosis
induced by trophic withdrawal in nerve growth factor-differentiated or
amyloid precursor protein-expressing PC12 cells. The apoptotic cell death
induced by PS2 protein was sensitive to pertussis toxin, suggesting that
heterotrimeric GTP-binding proteins are involved. A PS2 mutation
associated with familial Alzheimer's disease was found to generate a
molecule with enhanced basal apoptotic activity. This gain of function
might accelerate the process of neurodegeneration that occurs in
Alzheimer's disease, leading to the earlier age of onset characteristic of
familial Alzheimer's disease.

L19 ANSWER 12 OF 12 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:489438 BIOSIS
DN PREV199699211794
TI PS2 participates in cellular apoptosis.
AU ***Wolozin, B. (1)*** ; Vito, P.; Ganjei, K.; Iwasaki, K.; Lacana, E.;
D'Adamio, L.
CS (1) Section Geriatric Psychiatry, NIMH, NIAID, Bethesda, MD 20892 USA
SO Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 729.
Meeting Info.: 26th Annual Meeting of the Society for Neuroscience
Washington, D.C., USA November 16-21, 1996
ISSN: 0190-5295.
DT Conference
LA English

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E1      1   STERN CURTIS/AU
E2     11   STERN CURTIS H/AU
E3    527 --> STERN D/AU
E4     41   STERN D A/AU
E5    100   STERN D B/AU
E6    148   STERN D F/AU
E7     32   STERN D H/AU
E8      2   STERN D I/AU
E9     42   STERN D J/AU
E10    48   STERN D L/AU
E11   246   STERN D M/AU
E12    69   STERN D N/AU
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=> s e3

L20 527 "STERN D"/AU

=> s l20 and presenilin/ab,bi

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L21 1 L20 AND PRESENILIN/AB,BI

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L21 ANSWER 1 OF 1 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:527284 BIOSIS
DN PREV199799826487
TI ***Presenilin*** -2 couples with the signal transduction system of the
RAGE receptor.
AU Wolozin, B.; Alexander, P.; ***Stern, D.*** ; Schmidt, A. M.; Yan, S.
D.
CS Dep. Pharmacol., Loyola Univ. Chicago Med. Cent., Maywood, IL 60153 USA
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 1117.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience New
Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

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L22 56 L9

=> s l22 and neuron?/ab,bi

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L23 5 L22 AND NEURON?/AB,BI

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YOU HAVE REQUESTED DATA FROM 5 ANSWERS - CONTINUE? Y/(N):y

L24 ANSWER 1 OF 5 CAPLUS COPYRIGHT 1999 ACS
AN 1998:643914 CAPLUS
DN 130:50786
TI RAGE-A.beta. interactions in the pathophysiology of Alzheimer's disease
AU Yan, Shi Du; Stern, David; Kane, Michael D.; Kuo, Yu-Min; Lampert, Heather C.; Roher, Alex E.
CS Department of Pathology, Surgery, Medicine and Physiology, College of Physicians and Surgeons, Columbia University, New York, NY, 10032, USA
SO Restor. Neurol. Neurosci. (1998), 12(2,3), 167-173
CODEN: RNNEEL; ISSN: 0922-6028
PB IOS Press
DT Journal
LA English
AB RAGE is a cell surface mol. primarily identified for its capacity to bind advanced glycation end-products and amphoterin. Immunocytochem. studies demonstrated that in Alzheimer's disease (AD) the expression of RAGE is elevated in ***neurons*** close to neuritic plaque beta-amyloid (A.beta.) deposits and in the cells of A.beta. contg. vessels. Crosslinking of surface bound A.beta. 1-40 to endothelial cells, yielded a band of 50 kDa identified as RAGE. Using the sol. extracellular domain of recombinant human RAGE, we found that A.beta. binds to RAGE with a Kd = 57 nM, a value close to those found for mouse brain endothelial cells and rat cortical ***neurons*** . The interaction of A.beta. with RAGE in ***neuronal*** , endothelial, and RAGE-transfected COS-1 cells induced oxidative stress, as assessed by the TBARS and MTT assays. ELISA demonstrated a 2.5 times increase of RAGE in AD over control brains. Activated microglia also showed elevated expression of RAGE. In the BV-2 microglial cell line, RAGE bound A.beta. in a dose dependent manner with a Kd of 25 nM. Sol. A.beta. induced the migration of microglia along a concn. gradient, while immobilized A.beta. arrested this migration. A.beta.-RAGE interaction also activated NF-.kappa.B, resulting in ***neuronal*** up-regulation of macrophage-colony stimulating factor (M-CSF) which also induced microglial migration. Apparently, RAGE-A.beta. interactions play an important role in the pathophysiol. of Alzheimer's disease.

L24 ANSWER 2 OF 5 CAPLUS COPYRIGHT 1999 ACS
AN 1997:525836 CAPLUS
DN 127:204001
TI Binding of .beta.-amyloid protein by an ***advanced*** ***glycation*** ***end*** - ***product*** ***receptor*** and possible treatment of Alzheimer's disease
IN Stern, David; Schmidt, Ann Marie; Yan, Shi Du
PA Trustees of Columbia University, USA
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9726913	A1	19970731	WO 97-US857	19970121
W: AU, CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9718327	A1	19970820	AU 97-18327	19970121

PRAI US 96-592070 19960126
WO 97-US857 19970121
AB The .beta.-amyloid protein binds to a cell-surface RAGE (receptor for advanced glycation end products) in neural cells and induces neurotoxic damage typical of Alzheimer's disease. This interaction may be a useful target for treatment of Alzheimer's disease. Binding assays for the identification and characterization of .beta.-amyloid-binding proteins used to identify the interaction of .beta.-amyloid with RAGE are described. Peptides capable of inhibiting the interaction are reported.

L24 ANSWER 3 OF 5 CAPLUS COPYRIGHT 1999 ACS
AN 1997:544866 CAPLUS
DN 127:201264
TI Beta amyloid toxicity does not require RAGE protein
AU Liu, Y.; Dargusch, R.; Schubert, D.
CS The Salk Institute for Biological Studies, La Jolla, CA, 92037, USA
SO Biochem. Biophys. Res. Commun. (1997), 237(1), 37-40
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic
DT Journal
LA English
AB It has been suggested that a receptor for advanced glycation end products (RAGE) is the nerve cell receptor for amyloid .beta. protein (A.beta.). To det. if this is indeed the case, two neural cell lines as well as rat cortical ***neurons*** were examd. for the presence of the mRNA for RAGE by PCR and northern blot anal. Although lung was strongly pos., in no case was RAGE mRNA detected in the cultured neural cells. Glycated albumin is a major ligand for RAGE and the cell surface RAGE protein is trypsin sensitive. In agreement with the mRNA data, trypsin treatment did not alter A.beta. toxicity, nor did glycated albumin modify the A.beta. response. It follows that RAGE is not the neural receptor for A.beta..

L24 ANSWER 4 OF 5 CAPLUS COPYRIGHT 1999 ACS
AN 1995:898715 CAPLUS
DN 124:26311
TI The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin. Mediation of neurite outgrowth and co-expression of RAGE and amphoterin in the developing nervous system
AU Hori, Osamu; Brett, Jerold; Slattery, Timothy; Cao, Rong; Zhang, Jinghua; Chen, Jing Xian; Nagashima, Mariko; Lundh, Erik R.; Vijay, Sharmila; et al.
CS Coll. Physicians Surg., Columbia Univ., New York, NY, 10032, USA
SO J. Biol. Chem. (1995), 270(43), 25752-61
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The receptor of advanced glycation end products (RAGE), a newly-identified member of the Ig superfamily, mediates interactions of advanced glycation end product (AGE)-modified proteins with endothelium and other cell types. Survey of normal tissues demonstrated RAGE expression in situations in which accumulation of AGEs would be unexpected, leading to the hypothesis that under physiol. circumstances, RAGE might mediate interaction with ligands distinct from AGEs. Sequential chromatog. of bovine lung ext. identified polypeptides with Mr values of .apprxeq.12,000 (p12) and .apprxeq.23,000 (p23) which bound RAGE. NH2-terminal and internal protein sequence data for p23 matched that reported previously for amphoterin. Amphoterin purified from rat brain or recombinant rat amphoterin bound to purified sRAGE in a saturable and dose-dependent manner, blocked by anti-RAGE IgG or a sol. form of RAGE (sRAGE). Cultured embryonic rat

neurons , which express RAGE, displayed dose-dependent binding of
125I-amphoterin which was prevented by blockade of RAGE using antibody to
the receptor or excess sol. receptor (sRAGE). A functional correlate of
RAGE-amphoterin interaction was inhibition by anti-RAGE F(ab')2 and sRAGE
of neurite formation by cortical ***neurons*** specifically on
amphoterin-coated substrates. Consistent with a potential role for
RAGE-amphoterin interaction in development, amphoterin and RAGE
mRNA/antigen were co-localized in developing rat brain. These data
indicate that RAGE has physiol. relevant ligands distinct from AGEs which
are likely, via their interaction with the receptor, to participate the
physiol processes outside of the context of diabetes and accumulation of
AGEs.

L24 ANSWER 5 OF 5 CAPLUS COPYRIGHT 1999 ACS
AN 1994:240942 CAPLUS
DN 120:240942
TI Survey of the distribution of a newly characterized receptor for advanced
glycation end products in tissues
AU Brett, Jerold; Schmidt, Ann Marie; Yan, Shi Du; Zou, Yu Shan; Weidman,
Elliott; Pinsky, David; Nowygrod, Roman; Neeper, Michael; Przysiecki,
Craig; et al.
CS Coll. Physicians Surg., Columbia Univ., New York, NY, 10032, USA
SO Am. J. Pathol. (1993), 143(6), 1699-712
CODEN: AJPAA4; ISSN: 0002-9440
DT Journal
LA English
AB Advanced glycation end products (AGEs), the final products of non-enzymic
glycation and oxidn. of proteins, are found in the plasma and accumulate
in the tissues during aging and at an accelerated rate in diabetes. A
novel integral membrane protein, termed receptor for AGE (RAGE), forms a
central part of the cell surface binding site for AGEs. Using
monospecific, polyclonal antibody raised to human recombinant and bovine
RAGE, immunostaining of bovine tissues showed RAGE in the vasculature,
endothelium, and smooth muscle cells and in mononuclear cells in the
tissues. Consistent with these data, RAGE antigen and mRNA were
identified in cultured bovine endothelium, vascular smooth muscle, and
monocyte-derived macrophages. RAGE antigen was also visualized in bovine
cardiac myocytes as well as in cultures of neonatal rat cardiac myocytes
and in neural tissue where motor ***neurons*** , peripheral nerves, and
a population of cortical ***neurons*** were pos. In situ
hybridization confirmed the presence of RAGE mRNA in the tissues, and
studies with rat PC12 pheochromocytes indicated that they provide a
neuronal -related cell culture model for examg. RAGE expression.
Pathol. studies of human atherosclerotic plaques showed infiltration of
RAGE-expressing cells in the expanded intima. These results indicate that
RAGE is present in multiple tissues and suggest the potential relevance of
AGE-RAGE interactions for modulating properties of the vasculature as well
as neural and cardiac function, prominent areas of involvement in diabetes
and in the normal aging process.

=> s l9 and glial/ab,bi

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L25 1 L9 AND GLIAL/AB,BI

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L25 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1999 ACS
AN 1997:525836 CAPLUS
DN 127:204001
TI Binding of .beta.-amyloid protein by an ***advanced*** ***glycation*** ***end*** - ***product*** ***receptor*** and
possible treatment of Alzheimer's disease
IN Stern, David; Schmidt, Ann Marie; Yan, Shi Du
PA Trustees of Columbia University, USA
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9726913	A1	19970731	WO 97-US857	19970121
W: AU, CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9718327	A1	19970820	AU 97-18327	19970121
PRAI US 96-592070		19960126		
WO 97-US857		19970121		

=> d ab

L25 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1999 ACS
AB The .beta.-amyloid protein binds to a cell-surface RAGE (receptor for
advanced glycation end products) in neural cells and induces neurotoxic
damage typical of Alzheimer's disease. This interaction may be a useful
target for treatment of Alzheimer's disease. Binding assays for the
identification and characterization of .beta.-amyloid-binding proteins
used to identify the interaction of .beta.-amyloid with RAGE are
described. Peptides capable of inhibiting the interaction are reported.

=> s l9 and microglial/ab,bi

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L26 1 L9 AND MICROGLIAL/AB,BI

=> d

L26 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1999 ACS
AN 1998:643914 CAPLUS
DN 130:50786
TI RAGE-A.beta. interactions in the pathophysiology of Alzheimer's disease
AU Yan, Shi Du; Stern, David; Kane, Michael D.; Kuo, Yu-Min; Lampert, Heather
C.; Roher, Alex E.
CS Department of Pathology, Surgery, Medicine and Physiology, College of
Physicians and Surgeons, Columbia University, New York, NY, 10032, USA
SO Restor. Neurol. Neurosci. (1998), 12(2,3), 167-173
CODEN: RNNEEL; ISSN: 0922-6028
PB IOS Press
DT Journal
LA English

=> d ab

L26 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1999 ACS
AB RAGE is a cell surface mol. primarily identified for its capacity to bind

advanced glycation end-products and amphoterin. Immunocytochem. studies
demonstrated that in Alzheimer's disease (AD) the expression of RAGE is
elevated in neurons close to neuritic plaque beta-amyloid (A.beta.) deposits and in the cells of A.beta. contg. vessels. Crosslinking of surface bound A.beta. 1-40 to endothelial cells, yielded a band of 50 kDa
identified as RAGE. Using the sol. extracellular domain of recombinant
human RAGE, we found that A.beta. binds to RAGE with a Kd = 57 nM, a value
close to those found for mouse brain endothelial cells and rat cortical
neurons. The interaction of A.beta. with RAGE in neuronal, endothelial,
and RAGE-transfected COS-1 cells induced oxidative stress, as assessed by
the TBARS and MTT assays. ELISA demonstrated a 2.5 times increase of RAGE
in AD over control brains. Activated microglia also showed elevated
expression of RAGE. In the BV-2 ***microglial*** cell line, RAGE
bound A.beta. in a dose dependent manner with a Kd of 25 nM. Sol. A.beta.
induced the migration of microglia along a concn. gradient, while immobilized A.beta. arrested this migration. A.beta.-RAGE interaction
also activated NF-.kappa.B, resulting in neuronal up-regulation of macrophage-colony stimulating factor (M-CSF) which also induced ***microglial*** migration. Apparently, RAGE-A.beta. interactions play
an important role in the pathophysiol. of Alzheimer's disease.

=> s l9 and astrocyte#/ab,bi

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L27 1 L9 AND ASTROCYTE#/AB,BI

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L27 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1999 ACS
AN 1998:760707 CAPLUS
DN 130:107885
TI Cell activation by glycated proteins. AGE receptors, receptor recognition
factors and functional classification of AGEs
AU Thornalley, Paul J.
CS Department of Biological Sciences, University of Essex, Essex, CO4 3SQ, UK
SO Cell. Mol. Biol. (Paris) (1998), 44(7), 1013-1023
CODEN: CMOBEF; ISSN: 0145-5680
PB C.M.B. Association
DT Journal; General Review
LA English

=> s l9 and endothelial/ab,bi

'AB' IS NOT A VALID FIELD CODE
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2 FILES SEARCHED...
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
L28 18 L9 AND ENDOTHELIAL/AB,BI

=> dup rem l28

PROCESSING COMPLETED FOR L28
L29 15 DUP REM L28 (3 DUPLICATES REMOVED)

=> d l- bib ab

YOU HAVE REQUESTED DATA FROM 15 ANSWERS - CONTINUE? Y/(N):y

L29 ANSWER 1 OF 15 CAPLUS COPYRIGHT 1999 ACS
AN 1999:182259 CAPLUS
TI Characterization of the ***Advanced*** ***Glycation*** ***End***
- ***Product*** ***Receptor*** Complex in Human Vascular
Endothelial Cells
AU Stitt, Alan W.; He, Cijang; Vlassara, Helen
CS Department of Opthalmology, Royal Victoria Hospital, Queen's University of
Belfast, Belfast, BT12 6BA, UK
SO Biochem. Biophys. Res. Commun. (1999), 256(3), 549-556
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
AB Advanced glycation end products (AGEs) have been implicated as causal
factors in the vascular complications of diabetes and it is known that
these products interact with cells through specific receptors. The AGE-receptor complex, originally described as p60 and p90, has been
characterised in hemopoietic cells and the component proteins identified
and designated AGE-R1, -R2 and -R3. In the current study we have
characterised this receptor in human umbilical vein ***endothelial***
cells (HUVECs) and elucidated several important biol. properties which may
impact on AGE mediated vascular disease. 125I-AGE-BSA binding to HUVEC
monolayers was detd. with and without various cold competitors. The
synthetic AGE, 2-(2-furoyl)-4()-furanyl-1H-imidazole (FFI)-BSA, failed to
compete with AGE-BSA binding unlike observations already reported in
hemopoietic cells. The ability of 125I-AGE-BSA to bind to sepd. HUVEC
plasma membrane (PM) proteins was also examd. and the binding at specific
bands inhibited by antibodies to each component of the AGE-receptor
complex. Western blotting of whole cell and PM fractions, before and
after exposure to AGE-BSA, revealed that AGE-R1, -R2 and -R3 are subject
to upregulation upon exposure to their ligand, a phenomenon which was also
demonstrated by immunofluorescence of non-permeabilised cells. mRNA
expression of each AGE-receptor component was apparent in HUVECs, with the
AGE-R2 and -R3 gene expression being upregulated upon exposure to AGEs in
a time-dependent manner. A phosporylation assay in combination with
AGE-R2 immunopptn. demonstrated that this component of the receptor
complex is phosphorylated by acute exposure to AGE-BSA. These results
indicate the presence of a conserved AGE-receptor complex in vascular
endothelium which demonstrates subtle differences to other cell-types. In
response to AGE-modified mols., this complex is subject to upregulation,
while the AGE-R2 component also displays increased phosphorylation
possibly leading to enhanced signal transduction. (c) 1999 Academic
Press.

L29 ANSWER 2 OF 15 CAPLUS COPYRIGHT 1999 ACS
AN 1998:760707 CAPLUS
DN 130:107885
TI Cell activation by glycated proteins. AGE receptors, receptor recognition
factors and functional classification of AGEs
AU Thornalley, Paul J.
CS Department of Biological Sciences, University of Essex, Essex, CO4 3SQ, UK
SO Cell. Mol. Biol. (Paris) (1998), 44(7), 1013-1023
CODEN: CMOBEF; ISSN: 0145-5680
PB C.M.B. Association
DT Journal; General Review
LA English

AB A review, with .apprx.72 refs. Proteins modified by advanced glycation
end products (AGE) bind to cell surface receptors and other AGE binding
proteins. AGE-binding receptors are: scavenger receptors types I and II,
the receptor for advanced glycation end products (RAGE), oligosaccharyl
transferase-48 (OST-48, AGE-R1), 80K-H phosphoprotein (AGE-R2) and
galectin-3 (AGE-R3). AGE receptors are found in monocytes, macrophages,
endothelial cells, pericytes, podocytes, astrocytes and microglia.
AGE-modified proteins also bind to lysozyme and lactoferrin. A crit.
review of the evidence for receptors binding AGE-modified protein binding
in vivo is presented. Scavenger receptors have only been shown to bind
proteins modified by AGE to a much higher extent than found in vivo.
80K-H phosphoprotein is involved in FGFR3 signal transduction to MAP
kinase, and may be involved in AGE-receptor signal transduction. Whether
all of these proteins bind AGE-modified proteins in vivo is not yet clear.
Cell activation in response to AGE-modified proteins is assocd. with
increased expression of extracellular matrix proteins, vascular adhesion
mols., cytokines and growth factors. Depending on the cell type and
concurrent signaling, this is assocd. with chemotaxis, angiogenesis,
oxidative stress, cell proliferation or programmed cell death (PCD).
Receptor recognition factors for agonism at the AGE receptor have been
little studied but to date hydroimidazolones appear to be the most likely
candidates. Pharmacol. inhibition of AGE receptor-mediated cell
activation with specific antagonists may provide the basis for therapeutic
intervention in diseases where AGE accumulation is a suspected etiol.
factor vascular complications of diabetes, macrovascular disease, renal
insufficiency and Alzheimer's disease.

L29 ANSWER 3 OF 15 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1998:345185 BIOSIS
DN PREV199800345185
TI Differential expression of receptors for advanced glycation end products
on monocytes in patients with IDDM.
AU Festa, A.; Schmoelzer, B.; Schernthaner, G.; Menzel, E. J. (1)
CS (1) Dep. Immunol., Univ. Vienna, Borschkeg. 8A, A-1090 Vienna Austria
SO Diabetologia, (June, 1998) Vol. 41, No. 6, pp. 674-680.
ISSN: 0012-186X.
DT Article
LA English
AB Accelerated modification of proteins by glucose terminating in the
formation of advanced glycation endproducts (AGEs) is one of the main
pathogenetic mechanisms of diabetes-associated complications. One pathway
by which AGEs may exert their effects is by interaction with specific
receptors initially identified on macrophages, monocytes and
endothelial cells. As AGE-induced autocrine upregulation of AGE
receptors has been observed in vitro, we hypothesized that AGE-binding
might be enhanced in diabetic patients to compensate for the elevated
levels of circulating AGEs. We therefore examined the expression of
AGE-binding sites on peripheral monocytes, serum levels of AGEs and
AGE-induced cytokine production in patients with insulin-dependent
diabetes mellitus (IDDM) compared to age-matched, healthy control
subjects. In patients, AGE-binding capacity was significantly increased
and there was only one class of binding sites, as revealed by Scatchard
analysis (1.8 X 105 vs 1.4 X 105 binding sites per cell). Affinity of
binding was, however, similar (Ka 1.5 X 106 vs 1.4 X 106 mol-1).
Saturation of binding was reached at 2.0-3.0 mumol/l with AGE-bovine serum
albumin (BSA) as ligand. In contrast, cytometry using fluorescein
isothiocyanate-labelled AGE-proteins showed no saturability and
reversibility of AGE-binding up to 80 mumol/l, indicating non-specific
binding in this concentration range. Again, this non-specific binding was
significantly higher in IDDM patients. In addition, we found much higher
levels of circulating AGEs in patients as compared to controls and studied
possible functional consequences of increased AGE binding in vitro,
monocyte stimulation by AGEs triggering cytokine release to a similar
extent in patients and controls, i.e. independently of the AGE-binding
capacity. Our finding of an enhanced overall AGE-binding capacity of
peripheral monocytes in IDDM could be instrumental in limiting the plasma
concentration of AGEs, the non-specific binding coming into play after
saturation of specific binding sites by higher plasma AGE-levels. Both
binding strategies may act in concert as "damage limitation mechanisms" in
the development of AGE-dependent diabetic complications.

L29 ANSWER 4 OF 15 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998020373 EMBASE
TI American Diabetes Association Annual Meeting, 1997: ***Endothelial***
dysfunction, neuropathy and the diabetic foot, diabetic mastopathy, and
erectile dysfunction.
AU Bloomgarden Z.T.
SO Diabetes Care, (1998) 21/1 (183-189).
Refs: 5
ISSN: 0149-5992 CODEN: DICAD2
CY United States
DT Journal; Conference Article
FS 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LA English

L29 ANSWER 5 OF 15 CAPLUS COPYRIGHT 1999 ACS
AN 1998:643914 CAPLUS
DN 130:50786
TI RAGE-A.beta. interactions in the pathophysiology of Alzheimer's disease
AU Yan, Shi Du; Stern, David; Kane, Michael D.; Kuo, Yu-Min; Lampert, Heather
C.; Roher, Alex E.
CS Department of Pathology, Surgery, Medicine and Physiology, College of
Physicians and Surgeons, Columbia University, New York, NY, 10032, USA
SO Restor. Neurol. Neurosci. (1998), 12(2,3), 167-173
CODEN: RNNEEL; ISSN: 0922-6028
PB IOS Press
DT Journal
LA English
AB RAGE is a cell surface mol. primarily identified for its capacity to bind
advanced glycation end-products and amphoterin. Immunocytochem. studies
demonstrated that in Alzheimer's disease (AD) the expression of RAGE is
elevated in neurons close to neuritic plaque beta-amyloid (A.beta.)
deposits and in the cells of A.beta. contg. vessels. Crosslinking of
surface bound A.beta. 1-40 to ***endothelial*** cells, yielded a band
of 50 kDa identified as RAGE. Using the sol. extracellular domain of
recombinant human RAGE, we found that A.beta. binds to RAGE with a Kd = 57

nM, a value close to those found for mouse brain ***endothelial*** cells and rat cortical neurons. The interaction of A.beta. with RAGE in neuronal, ***endothelial*** , and RAGE-transfected COS-1 cells induced oxidative stress, as assessed by the TBARS and MTT assays. ELISA demonstrated a 2.5 times increase of RAGE in AD over control brains. Activated microglia also showed elevated expression of RAGE. In the BV-2 microglial cell line, RAGE bound A.beta. in a dose dependent manner with a Kd of 25 nM. Sol. A.beta. induced the migration of microglia along a concn. gradient, while immobilized A.beta. arrested this migration. A.beta.-RAGE interaction also activated NF-.kappa.B, resulting in neuronal up-regulation of macrophage-colony stimulating factor (M-CSF) which also induced microglial migration. Apparently, RAGE-A.beta. interactions play an important role in the pathophysiol. of Alzheimer's disease.

L29 ANSWER 6 OF 15 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:340038 BIOSIS
DN PREV199799639241
TI Characterization and functional analysis of the promoter of RAGE, the receptor for advanced glycation end products.
AU Li, Jianfeng; Schmidt, Ann Marie (1)
CS (1) Columbia Univ. Coll. Phys. Surg., 630 W. 168 St., P S 11-518, New York, NY 10032 USA
SO Journal of Biological Chemistry, (1997) Vol. 272, No. 26, pp. 16498-16506.
ISSN: 0021-9258.
DT Article
LA English
AB The receptor for advanced glycation end products, RAGE, is a member of the immunoglobulin superfamily of cell surface molecules differentially expressed on a range of cell types. Ligation of RAGE perturbs homeostatic mechanisms and, potentially, provides a basis for cellular dysfunction in pathologic situations in which its ligands accumulate. To understand factors underlying RAGE expression, we cloned the 5'-flanking region of the RAGE gene and characterized putative regulatory motifs. Analysis of the putative promoter region revealed the presence of three potential NF-kappa-B-like and two SP1 binding sites. Transient transfection of vascular ***endothelial*** and smooth muscle cells using chimeric 5'-deletion constructs linked to luciferase reporter revealed that the region -1543/-587 contributed importantly to both basal and stimulated expression of the RAGE gene. This region of the RAGE gene contained three putative NF-kappa-B-like binding sites and was responsible for increased luciferase activity observed when ***endothelial*** or smooth muscle cells were stimulated with lipopolysaccharide. DNase I footprinting assays and electrophoretic mobility shift assay revealed that two of the three NF-kappa-B-like binding sites (1 and 2) were likely functional and responsive to stimuli. Upon simultaneous mutation of NF-kappa-B-like sites 1 and 2, both basal promoter expression and response to stimulation with LPS, as measured by relative luciferase activity, were significantly diminished. These results point to NF-kappa-B-dependent mechanisms regulating cellular expression of RAGE and suggest a means of linking RAGE to the inflammatory response.

L29 ANSWER 7 OF 15 CAPLUS COPYRIGHT 1999 ACS
AN 1997:686811 CAPLUS
DN 127:344270
TI Advanced glycation end product (AGE)-mediated induction of tissue factor in cultured ***endothelial*** cells is dependent on RAGE
AU Bierhaus, Angelika; Illmer, Thomas; Kasper, Michael; Luther, Thomas; Quehenberger, Peter; Tritschler, Hans; Wahl, Peter; Ziegler, Reinhard; Muller, Martin; Nawroth, Peter P.
CS Department of Internal Medicine I, University of Heidelberg, Germany
SO Circulation (1997), 96(7), 2262-2271
CODEN: CIRCAZ; ISSN: 0009-7322
PB American Heart Association
DT Journal
LA English
AB Binding of advanced glycation end products (AGEs) to the cellular surface receptor (RAGE) induces translocation of the transcription factor NF-.kappa.B into the nucleus and NF-.kappa.B-mediated gene expression. This study examines the role of RAGE in the AGE albumin-mediated induction of ***endothelial*** tissue factor, known to be partly controlled by NF-.kappa.B. ***Endothelial*** cells (ECs) were incubated in the presence of an 18-mer phosphorothioate oligodeoxynucleotide antisense to the 5'-coding sequence of the RAGE gene (antisense RAGE; 0.1 .mu.mol/L). Sense oligonucleotides (sense RAGE, 0.1 .mu.mol/L) of the same region served as controls. The cellular uptake of oligonucleotides was controlled by immunofluorescence microscopy. RAGE transcription was suppressed by antisense RAGE, as demonstrated by RT-PCR reactions. AGE albumin-mediated activation of cultured ECs was studied after 48 h of preincubation of ECs with antisense or sense RAGE. Electrophoretic mobility shift assays and Western blot anal. demonstrated that the AGE albumin-induced translocation of NF-.kappa.B from the cytoplasm into the nucleus was suppressed in the presence of antisense RAGE but not by sense RAGE. In parallel, AGE albumin-mediated tissue factor transcription, activity, and antigen were significantly reduced in ECs exposed to antisense RAGE, whereas sense RAGE (and nonspecific oligonucleotides) did not influence tissue factor expression. In conclusion, activation of ECs and induction of tissue factor by AGE albumin in ECs is dependent on RAGE.

L29 ANSWER 8 OF 15 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:362973 BIOSIS
DN PREV199799654906
TI Advanced glycation end products and their receptors co-localise in rat organs susceptible to diabetic microvascular injury.
AU Soulis, T.; Thallas, V.; Youssef, S.; Gilbert, R. E.; McWilliam, R. G.; Murray-Mcintosh, R. P.; Cooper, M. E. (1)
CS (1) Dep. Med., Univ. Melbourne, Austin Australia
SO Diabetologia, (1997) Vol. 40, No. 6, pp. 619-628.
ISSN: 0012-186X.
DT Article
LA English
AB Advanced glycation end products (AGEs) are believed to play an important role in the development of diabetic complications. AGEs are increased in experimental diabetes and treatment with the inhibitor of advanced glycation end products, aminoguanidine, has been shown to attenuate the level of these products in tissues undergoing complications. Recently, an AGE-binding protein has been isolated from bovine lung ***endothelial*** cells and termed the receptor for advanced glycated end products

(RAGE).
The present study sought to determine the distribution of AGE and RAGE in
tissues susceptible to the long-term complications of diabetes including
the kidney, eye, nerve, arteries as well as in a tissue resistant to such
complications, the lung. Using polyclonal antisera both AGE and RAGE were
found to co-localize in the renal glomerulus. AGE staining was clearly
increased with age and was further increased by diabetes. Aminoguanidine
treatment reduced AGE accumulation in the kidney. Co-localization of AGE
and RAGE was demonstrated in the inner plexiform layer and the inner
limiting membrane of the retina and in nerve bundles from mesenteric
arteries. In the aorta, both AGE and RAGE were found in the intima, media
and adventitia. Medial staining was increased in diabetes and was reduced
by aminoguanidine treatment. A similar pattern was observed for RAGE in
the aorta. In the lung, RAGE was found widely distributed throughout the
lung whereas the distribution of AGE staining was more limited, primarily
localizing to macrophages. The co-localization of AGEs and RAGE in sites
of diabetic microvascular injury suggests that this ligand-receptor
interaction may represent an important mechanism in the genesis of
diabetic complications.

L29 ANSWER 9 OF 15 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:130388 BIOSIS
DN PREV199799422201
TI Advanced glycation end products (AGEs) co-localize with AGE receptors in
the retinal vasculature of diabetic and of AGE-infused rats.
AU Stitt, Alan W.; Li, Yong M.; Gardiner, Thomas A.; Bucala, Richard; Archer,
Desmond B.; Vlassara, Helen (1)
CS (1) Picower Inst. Med. Res., 350 Community Drive, Manhasset, NY 11030 USA
SO American Journal of Pathology, (1997) Vol. 150, No. 2, pp. 523-531.
ISSN: 0002-9440.
DT Article
LA English
AB Advanced glycation end products (AGEs), formed from the nonenzymatic
glycation of proteins and lipids with reducing sugars, have been
implicated in many diabetic complications; however, their role in diabetic
retinopathy remains largely unknown. Recent studies suggest that the
cellular actions of AGEs may be mediated by AGE-specific receptors
(AGE-R). We have examined the immunolocalization of AGEs and AGE-R
components R1 and R2 in the retinal vasculature at 2, 4, and 8 months
after STZ-induced diabetes as well as in nondiabetic rats infused with AGE
bovine serum albumin for 2 weeks. Using polyclonal or monoclonal anti-AGE
antibodies and polyclonal antibodies to recombinant AGE-R1 and AGE-R2,
immunoreactivity (IR) was examined in the complete retinal vascular tree
after isolation by trypsin digestion. After 2, 4, and 8 months of
diabetes, there was a gradual increase in AGE IR in basement membrane. At
8 months, pericytes, smooth muscle cells, and ***endothelial*** cells
of the retinal vessels showed dense intracellular AGE IR. AGE epitopes
stained most intensely within pericytes and smooth muscle cells but less
in basement membrane of AGE-infused rats compared with the diabetic group.
Retinas from normal or bovine-serum-albumin-infused rats were largely
negative for AGE IR. AGE-R1 and -R2 colocalized strongly with AGEs of
vascular ***endothelial*** cells, pericytes, and smooth muscle cells
of either normal, diabetic, or AGE-infused rat retinas, and this
distribution did not vary with each condition. The data indicate that AGEs
accumulate as a function of diabetes duration first within the basement
membrane and then intracellularly, co-localizing with cellular AGE-Rs.
Significant AGE deposits appear within the pericytes after long-term
diabetes or acute challenge with AGE infusion conditions associated with
pericyte damage. Co-localization of AGEs and AGE-Rs in retinal cells
points to possible interactions of pathogenic significance.

L29 ANSWER 10 OF 15 MEDLINE DUPLICATE 1
AN 97368045 MEDLINE
DN 97368045
TI Recombinant ***advanced*** ***glycation*** ***end***
product ***receptor*** pharmacokinetics in normal and diabetic
rats.
AU Renard C; Chappey O; Wautier M P; Nagashima M; Lundh E; Morser J; Zhao L;
Schmidt A M; Scherrmann J M; Wautier J L
CS Laboratoire de Recherche en Biologie Vasculaire et Cellulaire, Universite
Paris 7, Hopital Lariboisi'ere, France.
SO MOLECULAR PHARMACOLOGY, (1997 Jul) 52 (1) 54-62.
Journal code: NGR. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199710
EW 19971003
AB Vascular dysfunction in patients with diabetes mellitus is related to
advanced glycation end product (AGE) formation. We previously showed that
AGEs produce an increase in vascular permeability and generated an oxidant
stress after binding to the receptor (RAGE) present on endothelium. RAGE,
a 35-kDa protein that belongs to the immunoglobulin superfamily, has been
cloned from a rat lung cDNA library, and recombinant rat soluble RAGE
(rR-RAGE) has been produced in insect cells. The sequence of RAGE is
highly conserved between human and rat. We studied the biological effect
of rR-RAGE and pharmacokinetics of 125I-rR-RAGE after intravenous or
intraperitoneal administration in normal and streptozotocin-induced
diabetic rats. rR-RAGE prevented albumin or inulin transfer through a
bovine aortic ***endothelial*** cell monolayer, restored the
hyperpermeability observed in diabetic rats or induced in normal rats by
diabetic rat red blood cells, and corrected the reactive oxygen
intermediate production after intravenous or intraperitoneal
administration. After intravenous injection of 125I-rR-RAGE, the
distribution half-life was longer ($p < or = 0.01$) in diabetic (0.15 and
4.01 hr) than in normal (0.02 and 0.21 hr) rats, as was the case for the
elimination half-lives (diabetic, 57.17 hr; normal, 26.02 hr; $p < or = 0.01$). Distribution volume was higher in diabetic than in normal rats
(6.94 and 3.24 liter/kg, respectively; $p = 0.049$). Our study showed that
rR-RAGE was biologically active in vivo and slowly cleared, which suggests
it could be considered as a potential therapy.

L29 ANSWER 11 OF 15 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:98644 BIOSIS
DN PREV199799397847
TI A novel mechanism for the pathogenesis of diabetic retinopathy

involving
glucose-modified proteins.
AU Lambourne, B. J.; Molinatti, P. A.; Chibber, R.; Kohner, E. M.; Sonksen,
P. H.
CS Diabetic Retinopathy Unit, Div. Med., UMDS, St. Thomas' Hosp., London UK
SO International Journal of Microcirculation Clinical and Experimental,
(1996) Vol. 16, No. 4, pp. 214.
Meeting Info.: 1st Joint National Vascular Meeting of the British
Microcirculation Society, the British Society for Cardiovascular Research
and the Royal Society of Medicine Forum on Angiology Exeter, England, UK
April 17-19, 1996
ISSN: 0167-6865.
DT Conference; Abstract
LA English

L29 ANSWER 12 OF 15 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:375628 BIOSIS
DN PREV199699097984
TI A novel cellular receptor for advanced glycation end products.
AU Schmidt, Ann Marie (1); Hori, Osamu; Cao, Rong; Yan, Shi Du; Brett,
Jerold; Wautier, Jean-Luc; Ogawa, Satoshi; Kuwabara, Keisuke; Matsumoto,
Masayasu; Stern, David
CS (1) Dep. Physiol., P and S 11-518, Columbia Univ., Coll. Phys. Surg., 630
W. 168th, New York, NY 10032 USA
SO Diabetes, (1996) Vol. 45, No. SUPPL. 3, pp. S77-S80.
ISSN: 0012-1797.
DT Article
LA English
AB Exposure of proteins to reducing sugars results in nonenzymatic glycation
with the ultimate formation of advanced glycation end products (AGEs). One
means through which AGEs modulate cellular functions is through binding to
specific cell surface acceptor molecules. The receptor for AGEs (RAGE) is
such a receptor and is a newly identified member of the immunoglobulin
superfamily expressed on ***endothelial*** cells (ECs), mononuclear
phagocytes (MPs), and vascular smooth muscle cells (SMCs) in both vivo and
in vitro. Binding of AGEs to RAGE results in induction of cellular oxidant
stress, as exemplified by the generation of thiobarbituric acid-reactive
substances, expression of heme oxygenase type I, and activation of the
transcription factor NF-kappa-B, with consequences for a range of cellular
functions. AGEs on the surface of diabetic red cells enhance binding to
endothelial RAGE and result in enhanced oxidant stress in the
vessel wall. By using reagents to selectively block access to RAGE, the
role of this receptor in AGE-mediated perturbation of cellular properties
can be dissected in detail.

L29 ANSWER 13 OF 15 CAPLUS COPYRIGHT 1999 ACS
AN 1994:266466 CAPLUS
DN 120:266466
TI The ***endothelial*** cell binding site for advanced glycation end
products consists of a complex: an integral membrane protein and a
lactoferrin-like polypeptide
AU Schmidt, Ann Marie; Mora, Rozalia; Cao, Rong; Yan, Shi Du; Brett, Jerold;
Ramakrishnan, Rajasekhar; Tsang, T. Christopher; Simionescu, Maya; Stern,
David
CS Coll. Physicians Surg., Columbia Univ., New York, NY, 10032, USA
SO J. Biol. Chem. (1994), 269(13), 9882-8
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Advanced glycation end products (AGEs), formed as the result of the
extended interaction of proteins with ketoses, modulate central properties
of ***endothelial*** cells and mononuclear phagocytes by interacting
with a cell surface binding site comprised of a novel integral membrane
protein (receptor for AGE = RAGE) and a lactoferrin-like polypeptide
(LF-L), the latter having sequence identity to lactoferrin (LF). To
further understand this cellular binding site, the interaction of RAGE
with LF-L and LF was characterized. By ligand blotting and a solid state
competitive binding assay, 125I-LF-L and 125I-LF bound to RAGE immobilized
on nitrocellulose membranes or polypropylene tubes in a time-dependent and
reversible manner, demonstrating a high affinity component with Kd
.apprxeq. 100 pM. The interaction of 125I-LF-L and 125I-LF with RAGE was
independent of iron in LF and was competed by addn. of an excess of
unlabeled carboxyl-terminal portion of LF. Crosslinking studies with
purified 125I-LF-L and RAGE, in the presence of disuccinimidyl suberate,
showed a new, slowly migrating band, corresponding to a complex of RAGE
and LF-L, and crosslinking on mouse aortic ***endothelial*** cells
showed two new slowly migrating bands on immunoblotting visualized with
both anti-RAGE IgG and anti-LF-L IgG. These data lead the authors to
propose that the ***endothelial*** cell surface binding site for AGEs
consists of LF-L bound noncovalently to RAGE anchored in the cell
membrane.

L29 ANSWER 14 OF 15 CAPLUS COPYRIGHT 1999 ACS
AN 1994:531448 CAPLUS
DN 121:131448
TI Advanced glycation end products (AGEs) on the surface of diabetic
erythrocytes bind to the vessel wall via a specific receptor inducing
oxidant stress in the vasculature: a link between surface-associated AGEs
and diabetic complications
AU Wautier, J.-L.; Wautier, M.-P.; Schmidt, A.-M.; Anderson, G. M.; Hori, O.;
Zoukourian, C.; Capron, L.; Chappey, O.; Yan, S.-D.; et al.
CS Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1994), 91(16), 7742-6
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB Vascular complications are an important cause of morbidity and mortality
in patients with diabetes. The extent of vascular complications has been
linked statistically to enhanced adherence of diabetic erythrocytes to
endothelial cells (ECs) and to the accumulation of a class of
glycated proteins termed advanced glycation end products (AGEs). The
authors hypothesized that formation of AGEs on the surface of diabetic
erythrocytes could mediate their interaction with ECs leading to binding
and induction of vascular dysfunction. Enhanced binding of diabetic
erythrocytes to ECs was blocked by preincubation of erythrocytes with
anti-AGE IgG or preincubation of ECs with antibodies to the receptor for
AGE (RAGE). Immunoblotting of cultured human ECs and immunostaining of
normal/diabetic human tissue confirmed the presence of RAGE in the vessel

wall. Binding of diabetic erythrocytes to endothelium generated an oxidant stress, as measured by prodn. of thiobarbituric acid-reactive substances (TBARS) and activation of the transcription factor NF-.kappa.B, both of which were blocked by probucol or anti-RAGE IgG. Erythrocytes from diabetic rats infused into normal rats had an accelerated, early phase of clearance that was prevented, in part, by antibody to RAGE. Liver tissue from rats infused with diabetic erythrocytes showed elevated levels of TBARS, which was prevented by pretreatment with anti-RAGE IgG or probucol. Thus, erythrocyte surface AGEs can function as ligands that interact with RAGE on endothelium. The extensive contact of diabetic erythrocytes bearing surface-assocd. AGEs with vessel wall RAGE could be important in the development of vascular complications.

L29 ANSWER 15 OF 15 CAPLUS COPYRIGHT 1999 ACS
AN 1995:278135 CAPLUS
DN 122:233401
TI AGE-receptors and in vivo biological effects of AGEs
AU Vlassara, Helen
CS The Picower Institute for Medical Research, Manhasset/New York, 11030, USA
SO Spec. Publ. - R. Soc. Chem. (1994), 151(Maillard Reactions in Chemistry, Food, and Health), 254-61
CODEN: SROCDO; ISSN: 0260-6291
DT Journal; General Review
LA English
AB A review with 32 refs. on ***advanced*** ***glycation*** ***end*** ***product*** (AGE) ***receptors*** and the biol. effects of AGEs is presented. Surface receptors for AGEs are found on macrophages, T-lymphocytes, ***endothelial*** cells (EC), mesangial cells (MS), fibroblasts, and smooth muscle cells. Binding of AGEs to these receptors leads to a range of cellular responses including monocyte chemotaxis, activation, growth factor release, increased matrix prodn., increased EC permeability, and procoagulant activity. A no. of these responses can be inhibited by anti-AGE-receptor antibodies, supporting the role of AGE-ligand/receptor interactions in these events. Evidence for similar AGE-mediated biol. effects in vivo was obtained recently: short-term (4-8 wk) exogenous AGE administration to normal rats and rabbits led to multiple vascular defects including vascular permeability, mononuclear activation, and vasodilatory impairment. Longer treatment with AGEs (3 mo) led to arterial basement membrane thickening, mesangial expansion, and glomerulosclerotic changes. These alterations were largely prevented by simultaneous treatment with aminoguanidine. These studies suggest that the interaction of de novo implanted, reactive AGEs with cellular AGE-receptors of otherwise healthy tissues can generate renal, and vascular pathol. similar to that seen in diabetes, in the absence of either the genetic or the metabolic abnormalities linked to diabetes. Progressive loss of kidney function correlates with increasing circulating AGE levels, presumably reflecting tissue AGE-degrdn. products which are not cleared by the failing kidneys. The pronounced (.apprx.8-fold) increase in serum AGEs obsd. in diabetic anephric patients, a group particularly susceptible to accelerated atherosclerosis, indicates that uncleared "reactive" AGEs may be available for enhanced interaction with cellular AGE-receptors, accelerating existing pathol.

=> s l9 and mononuclear/ab,bi

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'AB' IS NOT A VALID FIELD CODE
4 FILES SEARCHED...
L30 6 L9 AND MONONUCLEAR/AB,BI

=> dup rem l30

PROCESSING COMPLETED FOR L30
L31 6 DUP REM L30 (0 DUPLICATES REMOVED)

=> d 1- bib ab

YOU HAVE REQUESTED DATA FROM 6 ANSWERS - CONTINUE? Y/(N):y

L31 ANSWER 1 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1997:525836 CAPLUS
DN 127:204001
TI Binding of .beta.-amyloid protein by an ***advanced*** ***glycation*** ***end*** - ***product*** ***receptor*** and possible treatment of Alzheimer's disease
IN Stern, David; Schmidt, Ann Marie; Yan, Shi Du
PA Trustees of Columbia University, USA
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9726913	A1	19970731	WO 97-US857	19970121
W: AU, CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9718327	A1	19970820	AU 97-18327	19970121
PRAI US 96-592070		19960126		
WO 97-US857		19970121		

AB The .beta.-amyloid protein binds to a cell-surface RAGE (receptor for advanced glycation end products) in neural cells and induces neurotoxic damage typical of Alzheimer's disease. This interaction may be a useful target for treatment of Alzheimer's disease. Binding assays for the identification and characterization of .beta.-amyloid-binding proteins used to identify the interaction of .beta.-amyloid with RAGE are described. Peptides capable of inhibiting the interaction are reported.

L31 ANSWER 2 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1996:552734 CAPLUS
DN 125:230717
TI The receptor for advanced glycation end products (RAGE) is a central mediator of the interaction of AGE-.beta.2microglobulin with human ***mononuclear*** phagocytes via an oxidant-sensitive pathway: implications for the pathogenesis of dialysis-related amyloidosis
AU Miyata, Toshio; Hori, Osamu; Zhang, JingHua; Yan, Shi Du; Ferran, Luis; Iida, Yoshiyasu; Schmidt, Ann Marie
CS Dep. Int. Med., Nagoya Univ. Sch. Med., Nagoya, 461, Japan
SO J. Clin. Invest. (1996), 98(5), 1088-1094
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
AB An important component of amyloid fibrils in dialysis-related amyloidosis is a form of .beta.2-microglobulin modified with advanced glycation end products (AGEs) of the Maillard reaction, known as AGE-.beta.2M. The authors demonstrate here that the interaction of AGE-.beta.2M with ***mononuclear*** phagocytes (MPs), cells important in the pathogenesis of the inflammatory arthropathy of dialysis-related amyloidosis, is mediated by the receptor for AGEs, or RAGE. 125I-AGE-.beta.2M

bound to
immobilized RAGE or to MPs in a specific, dose-dependent manner, a process
inhibited in the presence of RAGE blockade. AGE-.beta.2M-mediated
monocyte chemotaxis was prevented by excess sRAGE or anti-RAGE IgG.
Induction of tumor necrosis factor-.alpha. (TNF) expression by MPs exposed
to AGE-.beta.2M resulted from engagement of RAGE, as appearances of TNF
transcripts and TNF antigen release into culture supernatants were
prevented by addn. of sRAGE, a process mediated, at least in part, by
oxidant stress. AGE-.beta.2M reduced cytochrome c and the elaboration of
TNF by MPs was inhibited by N-acetylcysteine. Consistent with these data,
immunohistochem. studies of AGE-laden amyloid deposits of a long-term
hemodialysis patient reveals pos. staining for RAGE in the MPs
infiltrating these lesions. These data indicate that RAGE is a central
binding site for AGEs formed in vivo and suggest that AGE-.beta.2M-MP-RAGE
interaction likely contributes to the initiation of an inflammatory
response in amyloid deposits of long-term hemodialysis patients, a process
which may ultimately lead to bone and joint destruction.

L31 ANSWER 3 OF 6 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:375628 BIOSIS
DN PREV199699097984
TI A novel cellular receptor for advanced glycation end products.
AU Schmidt, Ann Marie (1); Hori, Osamu; Cao, Rong; Yan, Shi Du; Brett,
Jerold; Wautier, Jean-Luc; Ogawa, Satoshi; Kuwabara, Keisuke; Matsumoto,
Masayasu; Stern, David
CS (1) Dep. Physiol., P and S 11-518, Columbia Univ., Coll. Phys. Surg., 630
W. 168th, New York, NY 10032 USA
SO Diabetes, (1996) Vol. 45, No. SUPPL. 3, pp. S77-S80.
ISSN: 0012-1797.
DT Article
LA English
AB Exposure of proteins to reducing sugars results in nonenzymatic glycation
with the ultimate formation of advanced glycation end products (AGEs). One
means through which AGEs modulate cellular functions is through binding to
specific cell surface acceptor molecules. The receptor for AGEs (RAGE) is
such a receptor and is a newly identified member of the immunoglobulin
superfamily expressed on endothelial cells (ECs), ***mononuclear***
phagocytes (MPs), and vascular smooth muscle cells (SMCs) in both vivo and
in vitro. Binding of AGEs to RAGE results in induction of cellular oxidant
stress, as exemplified by the generation of thiobarbituric acid-reactive
substances, expression of heme oxygenase type I, and activation of the
transcription factor NF-kappa-B, with consequences for a range of cellular
functions. AGEs on the surface of diabetic red cells enhance binding to
endothelial RAGE and result in enhanced oxidant stress in the vessel wall.
By using reagents to selectively block access to RAGE, the role of this
receptor in AGE-mediated perturbation of cellular properties can be
dissected in detail.

L31 ANSWER 4 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1994:266466 CAPLUS
DN 120:266466
TI The endothelial cell binding site for advanced glycation end products
consists of a complex: an integral membrane protein and a lactoferrin-like
polypeptide
AU Schmidt, Ann Marie; Mora, Rozalia; Cao, Rong; Yan, Shi Du; Brett, Jerold;
Ramakrishnan, Rajasekhar; Tsang, T. Christopher; Simionescu, Maya; Stern,
David
CS Coll. Physicians Surg., Columbia Univ., New York, NY, 10032, USA
SO J. Biol. Chem. (1994), 269(13), 9882-8
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Advanced glycation end products (AGEs), formed as the result of the
extended interaction of proteins with ketoses, modulate central properties
of endothelial cells and ***mononuclear*** phagocytes by interacting
with a cell surface binding site comprised of a novel integral membrane
protein (receptor for AGE = RAGE) and a lactoferrin-like polypeptide
(LF-L), the latter having sequence identity to lactoferrin (LF). To
further understand this cellular binding site, the interaction of RAGE
with LF-L and LF was characterized. By ligand blotting and a solid state
competitive binding assay, 125I-LF-L and 125I-LF bound to RAGE immobilized
on nitrocellulose membranes or polypropylene tubes in a time-dependent and
reversible manner, demonstrating a high affinity component with Kd
.apprxeq. 100 pM. The interaction of 125I-LF-L and 125I-LF with RAGE was
independent of iron in LF and was competed by addn. of an excess of
unlabeled carboxyl-terminal portion of LF. Crosslinking studies with
purified 125I-LF-L and RAGE, in the presence of disuccinimidyl suberate,
showed a new, slowly migrating band, corresponding to a complex of RAGE
and LF-L, and crosslinking on mouse aortic endothelial cells showed two
new slowly migrating bands on immunoblotting visualized with both
anti-RAGE IgG and anti-LF-L IgG. These data lead the authors to propose
that the endothelial cell surface binding site for AGEs consists of LF-L
bound noncovalently to RAGE anchored in the cell membrane.

L31 ANSWER 5 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1995:278135 CAPLUS
DN 122:233401
TI AGE-receptors and in vivo biological effects of AGEs
AU Vlassara, Helen
CS The Picower Institute for Medical Research, Manhasset/New York, 11030, USA
SO Spec. Publ. - R. Soc. Chem. (1994), 151(Maillard Reactions in Chemistry,
Food, and Health), 254-61
CODEN: SROCDO; ISSN: 0260-6291
DT Journal; General Review
LA English
AB A review with 32 refs. on ***advanced*** ***glycation*** ***end*** ***product*** (AGE) ***receptors*** and the biol.
effects of AGEs is presented. Surface receptors for AGEs are found on
macrophages, T-lymphocytes, endothelial cells (EC), mesangial cells (MS),
fibroblasts, and smooth muscle cells. Binding of AGEs to these receptors
leads to a range of cellular responses including monocyte chemotaxis,
activation, growth factor release, increased matrix prodn., increased EC
permeability, and procoagulant activity. A no. of these responses can be
inhibited by anti-AGE-receptor antibodies, supporting the role of
AGE-ligand/receptor interactions in these events. Evidence for similar
AGE-mediated biol. effects in vivo was obtained recently: short-term (4-8
wk) exogenous AGE administration to normal rats and rabbits led

to
multiple vascular defects including vascular permeability, ***mononuclear*** activation, and vasodilatory impairment. Longer
treatment with AGEs (3 mo) led to arterial basement membrane thickening,
mesangial expansion, and glomerulosclerotic changes. These alterations
were largely prevented by simultaneous treatment with aminoguanidine.
These studies suggest that the interaction of de novo implanted, reactive
AGEs with cellular AGE-receptors of otherwise healthy tissues can generate
renal, and vascular pathol. similar to that seen in diabetes, in the
absence of either the genetic or the metabolic abnormalities linked to
diabetes. Progressive loss of kidney function correlates with increasing
circulating AGE levels, presumably reflecting tissue AGE-degrdn. products
which are not cleared by the failing kidneys. The pronounced
(.apprx.8-fold) increase in serum AGEs obsd. in diabetic anephric
patients, a group particularly susceptible to accelerated atherosclerosis,
indicates that uncleared "reactive" AGEs may be available for enhanced
interaction with cellular AGE-receptors, accelerating existing pathol.

L31 ANSWER 6 OF 6 CAPLUS COPYRIGHT 1999 ACS
AN 1994:240942 CAPLUS
DN 120:240942
TI Survey of the distribution of a newly characterized receptor for advanced
glycation end products in tissues
AU Brett, Jerold; Schmidt, Ann Marie; Yan, Shi Du; Zou, Yu Shan; Weidman,
Elliott; Pinsky, David; Nowygrod, Roman; Neeper, Michael; Przysiecki,
Craig; et al.
CS Coll. Physicians Surg., Columbia Univ., New York, NY, 10032, USA
SO Am. J. Pathol. (1993), 143(6), 1699-712
CODEN: AJPAA4; ISSN: 0002-9440
DT Journal
LA English
AB Advanced glycation end products (AGEs), the final products of non-enzymic
glycation and oxidn. of proteins, are found in the plasma and accumulate
in the tissues during aging and at an accelerated rate in diabetes. A
novel integral membrane protein, termed receptor for AGE (RAGE), forms a
central part of the cell surface binding site for AGEs. Using
monospecific, polyclonal antibody raised to human recombinant and bovine
RAGE, immunostaining of bovine tissues showed RAGE in the vasculature,
endothelium, and smooth muscle cells and in ***mononuclear*** cells in
the tissues. Consistent with these data, RAGE antigen and mRNA were
identified in cultured bovine endothelium, vascular smooth muscle, and
monocyte-derived macrophages. RAGE antigen was also visualized in bovine
cardiac myocytes as well as in cultures of neonatal rat cardiac myocytes
and in neural tissue where motor neurons, peripheral nerves, and a
population of cortical neurons were pos. In situ hybridization confirmed
the presence of RAGE mRNA in the tissues, and studies with rat PC12
pheochromocytes indicated that they provide a neuronal-related cell
culture model for examg. RAGE expression. Pathol. studies of human
atherosclerotic plaques showed infiltration of RAGE-expressing cells in
the expanded intima. These results indicate that RAGE is present in
multiple tissues and suggest the potential relevance of AGE-RAGE
interactions for modulating properties of the vasculature as well as
neural and cardiac function, prominent areas of involvement in diabetes
and in the normal aging process.

=> s l9 and tumor#/ab,bi

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L32 4 L9 AND TUMOR#/AB,BI

=> dup rem l32

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L33 4 DUP REM L32 (0 DUPLICATES REMOVED)

=> d 1- bib ab

YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):y

L33 ANSWER 1 OF 4 MEDLINE
AN 1999009111 MEDLINE
DN 99009111
TI A redox-triggered ras-effector interaction. Recruitment of
phosphatidylinositol 3'-kinase to Ras by redox stress.
AU Deora A A; Win T; Vanhaesebroeck B; Lander H M
CS Department of Biochemistry, Cornell University Medical College, New York,
New York 10021, USA.
NC GM55509 (NIGMS)
AI37637 (NIAID)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Nov 6) 273 (45) 29923-8.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199902
EW 19990204
AB Reactive free radical species are known to trigger biochemical events
culminating in transcription factor activation and modulation of gene
expression. The cytosolic signaling events triggered by free radicals that
result in nuclear responses are largely unknown. Here we identify a
signaling cascade triggered immediately upon redox activation of Ras. We
examined two physiologically relevant models of redox signaling: 1) nitric
oxide in human T cells, and 2) advanced glycation end product in rat
pheochromocytoma cells. Reactive free radical species generated by nitric
oxide donors and the interaction of ***advanced*** ***glycation***
end ***product*** with its ***receptor*** led to the
recruitment of p85/p110 phosphatidylinositol 3'-kinase (PI3K) to the
plasma membrane, where it associated directly with the effector domain of
Ras and became activated. Only the p110beta and p110delta (but not
p110alpha) catalytic subunits were recruited by redox-activated Ras.
Activation of downstream targets of PI3K such as protein kinase B/Akt and
mitogen-activated protein kinase was found to be PI3K dependent. Our study
demonstrates that nitrosative and oxidative stressors trigger
Ras-dependent and PI3K-regulated events in cells and define a biochemical
pathway that is triggered by redox signaling.

L33 ANSWER 2 OF 4 CAPLUS COPYRIGHT 1999 ACS
AN 1997:525836 CAPLUS
DN 127:204001
TI Binding of .beta.-amyloid protein by an ***advanced*** ***glycation*** ***end*** - ***product*** ***receptor*** and
possible treatment of Alzheimer's disease

IN Stern, David; Schmidt, Ann Marie; Yan, Shi Du
PA Trustees of Columbia University, USA
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE
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PI WO 9726913 A1 19970731 WO 97-US857 19970121
W: AU, CA, JP, MX
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AU 9718327 A1 19970820 AU 97-18327 19970121
PRAI US 96-592070 19960126
WO 97-US857 19970121
AB The .beta.-amyloid protein binds to a cell-surface RAGE (receptor for advanced glycation end products) in neural cells and induces neurotoxic damage typical of Alzheimer's disease. This interaction may be a useful target for treatment of Alzheimer's disease. Binding assays for the identification and characterization of .beta.-amyloid-binding proteins used to identify the interaction of .beta.-amyloid with RAGE are described. Peptides capable of inhibiting the interaction are reported.

L33 ANSWER 3 OF 4 CAPLUS COPYRIGHT 1999 ACS
AN 1996:552734 CAPLUS
DN 125:230717
TI The receptor for advanced glycation end products (RAGE) is a central mediator of the interaction of AGE-.beta.2microglobulin with human mononuclear phagocytes via an oxidant-sensitive pathway: implications for the pathogenesis of dialysis-related amyloidosis
AU Miyata, Toshio; Hori, Osamu; Zhang, JingHua; Yan, Shi Du; Ferran, Luis; Iida, Yoshiyasu; Schmidt, Ann Marie
CS Dep. Int. Med., Nagoya Univ. Sch. Med., Nagoya, 461, Japan
SO J. Clin. Invest. (1996), 98(5), 1088-1094
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
AB An important component of amyloid fibrils in dialysis-related amyloidosis is a form of .beta.2-microglobulin modified with advanced glycation end products (AGEs) of the Maillard reaction, known as AGE-.beta.2M. The authors demonstrate here that the interaction of AGE-.beta.2M with mononuclear phagocytes (MPs), cells important in the pathogenesis of the inflammatory arthropathy of dialysis-related amyloidosis, is mediated by the receptor for AGEs, or RAGE. 125I-AGE-.beta.2M bound to immobilized RAGE or to MPs in a specific, dose-dependent manner, a process inhibited in the presence of RAGE blockade. AGE-.beta.2M-mediated monocyte chemotaxis was prevented by excess sRAGE or anti-RAGE IgG. Induction of ***tumor*** necrosis factor-.alpha. (TNF) expression by MPs exposed to AGE-.beta.2M resulted from engagement of RAGE, as appearances of TNF transcripts and TNF antigen release into culture supernatants were prevented by addn. of sRAGE, a process mediated, at least in part, by oxidant stress. AGE-.beta.2M reduced cytochrome c and the elaboration of TNF by MPs was inhibited by N-acetylcysteine. Consistent with these data, immunohistochem. studies of AGE-laden amyloid deposits of a long-term hemodialysis patient reveals pos. staining for RAGE in the MPs infiltrating these lesions. These data indicate that RAGE is a central binding site for AGEs formed in vivo and suggest that AGE-.beta.2M-MP-RAGE interaction likely contributes to the initiation of an inflammatory response in amyloid deposits of long-term hemodialysis patients, a process which may ultimately lead to bone and joint destruction.

L33 ANSWER 4 OF 4 MEDLINE
AN 95096076 MEDLINE
DN 95096076
TI Receptor-mediated endocytic uptake of methylglyoxal-modified serum albumin. Competition with advanced glycation end product-modified serum albumin at the ***advanced*** ***glycation*** ***end*** ***product*** ***receptor***
AU Westwood M E; McLellan A C; Thornalley P J
CS Department of Chemistry and Biological Chemistry, University of Essex, Colchester, United Kingdom.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Dec 23) 269 (51) 32293-8.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199503
AB Methylglyoxal binds and irreversibly modifies arginine and lysine residues in bovine serum albumin (BSA) under physiological conditions, producing a protein with an increased net negative charge at physiological pH. At 4 degrees C, methylglyoxal-modified BSA (MG-BSA) was bound by cell surface receptors on murine P388D1 macrophages. The apparent dissociation constant KD value was 435 +/- 2 nM, and there were 8.89 +/- 0.02 x 10(5) receptors/cell (n = 6), compare with an apparent KD value of 263 +/- 52 nM and 10.17 +/- 0.93 x 10(5) receptors/cell (n = 11) for advanced glycation end product-modified BSA (AGE-BSA). AGE-BSA competed with MG-BSA for binding to a common receptor; however, a component of AGE-BSA receptor binding could not be displaced by MG-BSA, and a component of MG-BSA receptor binding could not be displaced by AGE-BSA, suggesting that there are binding sites for both AGE-BSA and MG-BSA, competitive and noncompetitive, to MG-BSA and AGE-BSA on P388D1 cells at 4 degrees C. At 37 degrees C, receptor binding of AGE-BSA and MG-BSA was followed by endocytosis and lysosomal degradation of the modified protein. Methylglyoxal-modified proteins are ligands for the AGE receptor, and their formation and metabolism may be linked to the development of diabetic complications.

=> s l9 and pc12/ab,bi

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L34 2 L9 AND PC12/AB,BI

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L35 2 DUP REM L34 (0 DUPLICATES REMOVED)

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YOU HAVE REQUESTED DATA FROM 2 ANSWERS - CONTINUE? Y/(N):y

L35 ANSWER 1 OF 2 CAPLUS COPYRIGHT 1999 ACS
AN 1997:544866 CAPLUS
DN 127:201264

TI Beta amyloid toxicity does not require RAGE protein
AU Liu, Y.; Dargusch, R.; Schubert, D.
CS The Salk Institute for Biological Studies, La Jolla, CA, 92037, USA
SO Biochem. Biophys. Res. Commun. (1997), 237(1), 37-40
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic
DT Journal
LA English
AB It has been suggested that a receptor for advanced glycation end products
(RAGE) is the nerve cell receptor for amyloid .beta. protein (A.beta.).
To det. if this is indeed the case, two neural cell lines as well as rat
cortical neurons were examd. for the presence of the mRNA for RAGE by PCR
and northern blot anal. Although lung was strongly pos., in no case was
RAGE mRNA detected in the cultured neural cells. Glycated albumin is a
major ligand for RAGE and the cell surface RAGE protein is trypsin
sensitive. In agreement with the mRNA data, trypsin treatment did not
alter A.beta. toxicity, nor did glycated albumin modify the A.beta.
response. It follows that RAGE is not the neural receptor for A.beta..

L35 ANSWER 2 OF 2 CAPLUS COPYRIGHT 1999 ACS
AN 1994:240942 CAPLUS
DN 120:240942
TI Survey of the distribution of a newly characterized receptor for advanced
glycation end products in tissues
AU Brett, Jerold; Schmidt, Ann Marie; Yan, Shi Du; Zou, Yu Shan; Weidman,
Elliott; Pinsky, David; Nowygrod, Roman; Neeper, Michael; Przysiecki,
Craig; et al.
CS Coll. Physicians Surg., Columbia Univ., New York, NY, 10032, USA
SO Am. J. Pathol. (1993), 143(6), 1699-712
CODEN: AJPAA4; ISSN: 0002-9440
DT Journal
LA English
AB Advanced glycation end products (AGEs), the final products of non-enzymic
glycation and oxidn. of proteins, are found in the plasma and accumulate
in the tissues during aging and at an accelerated rate in diabetes. A
novel integral membrane protein, termed receptor for AGE (RAGE), forms a
central part of the cell surface binding site for AGEs. Using
monospecific, polyclonal antibody raised to human recombinant and bovine
RAGE, immunostaining of bovine tissues showed RAGE in the vasculature,
endothelium, and smooth muscle cells and in mononuclear cells in the
tissues. Consistent with these data, RAGE antigen and mRNA were
identified in cultured bovine endothelium, vascular smooth muscle, and
monocyte-derived macrophages. RAGE antigen was also visualized in bovine
cardiac myocytes as well as in cultures of neonatal rat cardiac myocytes
and in neural tissue where motor neurons, peripheral nerves, and a
population of cortical neurons were pos. In situ hybridization confirmed
the presence of RAGE mRNA in the tissues, and studies with rat
PC12 pheochromocytes indicated that they provide a
neuronal-related cell culture model for examg. RAGE expression. Pathol.
studies of human atherosclerotic plaques showed infiltration of
RAGE-expressing cells in the expanded intima. These results indicate that
RAGE is present in multiple tissues and suggest the potential relevance of
AGE-RAGE interactions for modulating properties of the vasculature as well
as neural and cardiac function, prominent areas of involvement in diabetes
and in the normal aging process.

=> s l1 and pc12/ab,bi

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'AB' IS NOT A VALID FIELD CODE
L36 88 L1 AND PC12/AB,BI

=> s l36 and l9

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'AB' IS NOT A VALID FIELD CODE
L37 0 L36 AND L9

=> s l1 and tumor#/ab,bi

'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
3 FILES SEARCHED...
'AB' IS NOT A VALID FIELD CODE
L38 37 L1 AND TUMOR#/AB,BI

=> dup rem l38

PROCESSING COMPLETED FOR L38
L39 31 DUP REM L38 (6 DUPLICATES REMOVED)

=> d 1- bib ab

YOU HAVE REQUESTED DATA FROM 31 ANSWERS - CONTINUE? Y/(N):y

L39 ANSWER 1 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1999:96387 CAPLUS
DN 130:164015
TI Characterization of transcription factor Sel-10 and its use in drug screening
IN Greenwald, Iva; Hubbard, E. Jane
PA The Trustees of Columbia University in the City of New York, USA
SO PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9905307	A1	19990204	WO 98-US15335	19980723

W: AU, CA, JP, MX, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRAI US 97-899578 19970724
AB This invention provides a cDNA sequence of the Sel-10 gene and the transcription factor thus encoded, which appears to be a member of the Cdc4 family of proteins. Genetic evidence indicates that Sel-10 is a neg. regulator of lin-12 mediated signaling in C. elegans, whereby lin-12 activity is controlled by controlling lin-12/Notch protein levels. Since Notch can induce mammalian ***tumors*** and since sel-10 downregulates Notch activity, it is suggested that sel-10 behaves as a ***tumor*** suppressor. This invention further provides methods for identifying compds. that are capable of treating cancer and Alzheimer's disease.

L39 ANSWER 2 OF 31 MEDLINE
AN 1999101168 MEDLINE
DN 99101168
TI Dual roles of proteasome in the metabolism of ***presenilin*** 1.
AU Honda T; Yasutake K; Nihonmatsu N; Mercken M; Takahashi H; Murayama O; Murayama M; Sato K; Omori A; Tsubuki S; Saido T C; Takashima A
CS Laboratory for Alzheimer's Disease, Brain Science Institute, RIKEN, Saitama, Japan.

SO JOURNAL OF NEUROCHEMISTRY, (1999 Jan) 72 (1) 255-61.
Journal code: JAV. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
EW 19990304
AB ***Presenilin*** 1 (PS1) has been identified as a causative gene for most early-onset familial Alzheimer's disease. Biochemical studies revealed that PS1 exists predominantly as two processed fragments in cells and brain tissues. We prepared stably transfected cells expressing the wild-type and familial Alzheimer's disease-associated mutants of PS1 and investigated the enzyme that participates in the metabolism of PS1. After treatment of the cells with proteasome inhibitors, the full-length PS1 was significantly accumulated. The levels of N- and C-terminal fragments were also increased. The accumulation of PS1 with a deletion of exon 10, which is unable to be processed, on treatment of the transfected cells with lactacystin indicated that proteasome can degrade full-length PS1. A synthetic peptide that includes the processing region of PS1 was cleaved by 20S proteasome at the putative processing sites after Met288 and Glu299. Metabolic labeling experiments showed that the appearance of the N-terminal fragment was attenuated by the inhibitor. Finally, 28-kDa N- and 20-kDa C-terminal fragments were generated by purified PS1 in vitro. These data indicated that the proteasome pathway is involved in PS1 processing. These results demonstrate that the proteasome pathway plays dual roles in processing and degradation of PS1.

L39 ANSWER 3 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1998:682417 CAPLUS
DN 129:286713
TI Diagnosis of genetic disease arising from frameshift mutation by RT-PCR and hybridization or antibody assay, and treatment with hammerhead ribozyme cleavage of defective mRNA
IN Van Leeuwen, Frederik W.; Grosveld, Franklin G.; Burbach, Johannes Peter Henri
PA Royal Netherlands Academy of Arts and Sciences, Neth.; Erasmus University Rotterdam; University of Utrecht
SO PCT Int. Appl., 258 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9845322	A2	19981015	WO 98-IB705	19980402
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9870715	A1	19981030	AU 98-70715	19980402
PRAI US 97-43163		19970410		
WO 98-IB705		19980402		

AB The invention relates to methods and reagents for the diagnosis of a diseases, specifically neurodegenerative diseases, caused by or assocd. with frameshift mutations, by RT-PCR and nucleic acid probe hybridization or by antibody detection of disease protein epitopes, and for treating these diseases via ribozyme cleavage of the mutant mRNA. The diagnostic methods include the steps of providing a body fluid or tissue sample from a patient, and analyzing the sample for the presence of an RNA mol. having a frameshift mutation or a protein encoded thereby, wherein the presence of the mutated RNA mol. or encoded protein is indicative of the disease. The therapeutic treatments include administering substances which selectively eliminate mutated RNA mol. from the cell, such as a genetic construct which provides for the synthesis of a ribozyme capable of selective cleavage of the mutant RNA. Neurodegenerative diseases such as Alzheimer's disease Down's syndrome are preferred examples to which these diagnostic and therapeutic method may be applied.

L39 ANSWER 4 OF 31 MEDLINE
AN 1999069372 MEDLINE
DN 99069372
TI Abrogation of the ***presenilin*** 1/beta-catenin interaction and preservation of the heterodimeric ***presenilin*** 1 complex following caspase activation.
AU Tesco G; Kim T W; Diehlmann A; Beyreuther K; Tanzi R E
CS Genetics and Aging Unit, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129, USA.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Dec 18) 273 (51) 33909-14.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199903
EW 19990305
AB beta-Catenin has previously been shown to interact with ***presenilin*** 1 (PS1) in transfected cells. Here we report that beta-catenin co-immunoprecipitates with the endogenous C-terminal fragment of ***presenilin*** 1 (PS1-CTF) but not with the endogenous CTF of ***presenilin*** 2 (PS2-CTF) in H4 human neuroglioma cells. During staurosporine (STS)-induced cell death, beta-catenin and PS1-CTF undergo a caspase-mediated cleavage. After 12 h of STS treatment, the beta-catenin.PS1-CTF interaction is abrogated. While PS1-CTF immunoprecipitated with all caspase-cleaved species of beta-catenin, beta-catenin holoprotein did not co-immunoprecipitate with the "alternative" caspase-derived PS1-CTF (PS1-aCTF). Thus, the abrogation of the beta-catenin.PS1-CTF complex was due to caspase cleavage of PS1-CTF. beta-Catenin co-immunoprecipitated with PS1-NTF, but only when PS1-NTF was associated with PS1-CTF. Even though PS1-NTF.CTF complex stability was not altered by caspase cleavage, its ability to bind beta-catenin was abolished. Thus, while the PS1-NTF.CTF complex is preserved after caspase cleavage, it may no longer be fully functional.

L39 ANSWER 5 OF 31 MEDLINE
AN 1999047359 MEDLINE
DN 99047359
TI Prominent expression of ***presenilin*** -1 in senile plaques and reactive astrocytes in Alzheimer's disease brain.
AU Weggen S; Diehlmann A; Buslei R; Beyreuther K; Bayer T A
CS Department of Psychiatry, University of Bonn Medical Center, Germany.
SO NEUROREPORT, (1998 Oct 5) 9 (14) 3279-83.

Journal code: A6M. ISSN: 0959-4965.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
EW 19990304
AB Mutations in the ***presenilin*** 1 (PS-1) gene account for most cases of autosomal dominant early-onset familial Alzheimer's disease (AD). In order to elucidate the cellular expression profile of PS-1 we used a novel N-terminal monoclonal antibody against human PS-1. Immunohistochemical staining was observed strongly in senile plaques, and reactive astrocytes of gray and white matter. Neuronal immunoreactivity, however, was found to be only moderate. RT-PCR analysis of PS-1 mRNA revealed expression throughout human development as well as in human glioma cell lines. Altered PS-1 function may contribute to plaque formation in AD.

L39 ANSWER 6 OF 31 MEDLINE
AN 1998421807 MEDLINE
DN 98421807
TI ***Presenilin*** 1 mutations linked to familial Alzheimer's disease increase the intracellular levels of amyloid beta-protein 1-42 and its N-terminally truncated variant(s) which are generated at distinct sites.
AU Sudoh S; Kawamura Y; Sato S; Wang R; Saido T C; Oyama F; Sakaki Y; Komano H; Yanagisawa K
CS Department of Dementia Research, National Institute for Longevity Sciences, Obu, Aichi, Japan.
SO JOURNAL OF NEUROCHEMISTRY, (1998 Oct) 71 (4) 1535-43.
Journal code: JAV. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
AB Mutations in the ***presenilin*** genes PS1 and PS2 cause the most common form of early-onset familial Alzheimer's disease. The influence of PS1 mutations on the generation of endogenous intracellular amyloid beta-protein (A beta) species was assessed using a highly sensitive immunoblotting technique with inducible mouse neuroblastoma (Neuro 2a) cell lines expressing the human wild-type (wt) or mutated PS1 (M146L or delta exon 10). The induction of mutated PS1 increased the intracellular levels of two distinct A beta species ending at residue 42 that were likely to be A beta1-42 and its N-terminally truncated variant(s) A beta x-42. The induction of mutated PS1 resulted in a higher level of intracellular A beta1-42 than of intracellular A beta x-42, whereas extracellular levels of A beta1-42 and A beta x-42 were increased proportionally. In addition, the intracellular generation of these A beta42 species in wt and mutated PS1-induced cells was completely blocked by brefeldin A, whereas it exhibited differential sensitivities to monensin: the increased accumulation of intracellular A beta x-42 versus inhibition of intracellular A beta1-42 generation. These data strongly suggest that A beta x-42 is generated in a proximal Golgi, whereas A beta1-42 is generated in a distal Golgi and/or a post-Golgi compartment. Thus, it appears that PS1 mutations enhance the degree of 42-specific gamma-secretase cleavage that occurs in the normal beta-amyloid precursor protein processing pathway (a) in the endoplasmic reticulum or the early Golgi apparatus prior to beta-secretase cleavage or (b) in the distinct sites where A beta x-42 and A beta1-42 are generated.

L39 ANSWER 7 OF 31 MEDLINE
AN 1998294913 MEDLINE
DN 98294913
TI Caspase-mediated cleavage is not required for the activity of ***presenilins*** in amyloidogenesis and NOTCH signaling.
AU Brockhaus M; Grunberg J; Rohrig S; Loetscher H; Wittenburg N; Baumeister R; Jacobsen H; Haass C
CS F. Hoffmann-LaRoche Ltd, Pharma Division, Preclinical CNS Research-Gene Technology, Basel, Switzerland.
SO NEUROREPORT, (1998 May 11) 9 (7) 1481-6.
Journal code: A6M. ISSN: 0959-4965.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199810
EW 19981005
AB The Alzheimer's disease (AD) associated ***presenilin*** (PS) proteins are proteolytically processed. One of the processing pathways involves cleavage by caspases. Pharmacological inhibition of caspases is currently being discussed as a treatment for a variety of neurodegenerative diseases, including AD. We therefore inhibited caspase mediated processing of PS-1 and PS-2 in cells transfected with wt and mutant PS by mutagenizing the substrate recognition site or by using specific peptide aldehydes known to block caspases. We found that the inhibition of caspase mediated processing of PS proteins does not decrease its amyloidogenic activity. PS cDNA constructs with mutations in the caspase cleavage site are biologically active in Caenorhabditis elegans such as the wt human PS proteins, demonstrating that caspase-mediated cleavage is not required for the physiological PS function in NOTCH signaling.

L39 ANSWER 8 OF 31 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 1
AN 1998240134 EMBASE
TI Inhibition of ***presenilin*** 1 expression is promoted by p53 and p21(WAF-1) and results in apoptosis and ***tumor*** suppression.
AU Roperch J.-P.; Alvaro V.; Prieur S.; Tuynder M.; Nemani M.; Lethrosne F.; Piouffre L.; Gendron M.-C.; Israeli D.; Dausset J.; Oren M.; Amson R.; Telerman A.
CS A. Telerman, Fondation Jean Dausset-CEPH, 27 rue Juliette Dodu, 75010 Paris, France. Telerman@cephb.fr
SO Nature Medicine, (1998) 4/7 (835-838).
Refs: 20
ISSN: 1078-8956 CODEN: NAMEFI
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
022 Human Genetics
LA English
SL English
AB Previously, we cloned a cDNA fragment, TSIP 2 (***tumor*** suppressor inhibited pathway clone 2), that detects by northern blot analysis of M1-LTR6 cells a 3-kb mRNA downregulated during p53-induced apoptosis. Cloning the full-length TSIP 2 cDNA showed that it corresponds to the ***presenilin*** 1 (PS1) gene, in which mutations have been reported in early-onset familial Alzheimer's disease. Here we demonstrate that PS1 is downregulated in a series of model systems for p53-dependent and p53-independent apoptosis and ***tumor*** suppression. To investigate the biological relevance of this downregulation, we stably transfected

U937 cells with antisense PS1 cDNA. The downregulation of PS1 in these
U937 transfectants results in reduced growth with an increased fraction of
the cells in apoptosis. When injected into mice homozygous for severe
combined immunodeficiency disease (scid/scid mice), these cells show a
suppression of their malignant phenotype. Our results indicate that PS1,
initially identified in a neurodegenerative disease, may also be involved
in the regulation of cancer-related pathways.

L39 ANSWER 9 OF 31 MEDLINE
AN 1998330911 MEDLINE
DN 98330911
TI Stable association of ***presenilin*** derivatives and absence of
presenilin interactions with APP.
AU Thinakaran G; Regard J B; Bouton C M; Harris C L; Price D L; Borchelt D R;
Sisodia S S
CS Department of Pathology, Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205-2196.
NC 1PO1 AG 14248 (NIA)
5 P50 AG 05146 (NIA)
SO NEUROBIOLOGY OF DISEASE, (1998 Apr) 4 (6) 438-53.
Journal code: CUN. ISSN: 0969-9961.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199811
EW 19981104
AB Mutations in two related genes, ***presenilin*** 1 and 2
presenilin 2 (PS1 and PS2), cosegregate with Alzheimer's disease.
PS1 and PS2 are highly homologous polytopic membrane proteins that are
subject to endoproteolytic cleavage in vivo. The resulting N- and
C-terminal derivatives are the preponderant PS-related species that
accumulate in cultured cells and tissue. In earlier studies, we
demonstrated that PS1 N- and C-terminal derivatives accumulate to 1:1
stoichiometry and that the absolute levels of fragments are established by
a tightly regulated and saturable mechanism. These findings led to the
suggestion that the levels of PS1 derivatives might be determined by their
association with limiting cellular components. In this study, we use in
situ chemical cross-linking and coimmunoprecipitation analyses to document
that the N- and C-terminal derivatives of either PS1 or PS2 can be
coisolated. Moreover, and in contrast to published reports which
documented that PS1 and PS2 form stable heteromeric assemblies with the
beta-amyloid precursor protein (APP), we have failed to provide evidence
for physiological complexes between PS1 and PS2 holoproteins or their
derivatives with APP.

L39 ANSWER 10 OF 31 MEDLINE
AN 1998363099 MEDLINE
DN 98363099
TI Effect of steroid receptors, pS2 and cathepsin D on the outcome of elderly
breast cancer patients: an exploratory investigation.
AU Coradini D; Biganzoli E; Boracchi P; Bombardieri E; Seregni E; De Palo G;
Martelli G; Di Fronzo G
CS Division of Experimental Oncology C, Istituto Nazionale per lo Studio e la
Cura dei Tumori, Milan, Italy.. coradini@istitutotumori.mi.it
SO INTERNATIONAL JOURNAL OF CANCER, (1998 Aug 21) 79 (4) 305-11.
Journal code: GQU. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199810
EW 19981004
AB In 83 elderly breast cancer patients, oestrogen and progesterone receptors
(ER, PgR), pS2 and cathepsin D (CathD) were evaluated for their possible
prognostic role on disease-free survival (DFS). The biomarkers were
determined on the same cytosol by using immunoradiometric assays, and the
variables were considered on a continuous scale. Univariate analysis
indicated a linear relationship between logarithmic hazard ratio (log(HR))
and the log(ER) and log(PgR) concentration, but a non-linear relationship
between log(HR) and CathD. As regards pS2, there was no evidence of a
relationship with log(HR). In multivariate analysis, log(ER) content did
not have a significant prognostic role, whereas log(PgR) retained a
significant prognostic role. As regards the predictive ability, log(PgR)
was the best discriminator of outcome followed by CathD, whereas the
contribution of log(ER) was negligible. In multivariate analysis, 2 models
were considered: one with log(ER), pS2, CathD and the interaction between
pS2 and CathD, and another with log(PgR), pS2, CathD and the interaction
between pS2 and CathD. In the first model, log(ER) content did not have a
significant prognostic role, whereas in the second model log(PgR) retained
a significant prognostic role. Our findings indicate that the quantitative
determination of pS2 and CathD, in addition to steroid receptors, on the
same cytosolic fraction could be a complementary tool to describe all
breast cancer patients rather than just the elderly and that the use of a
continuous scale, instead of a simple dichotomous "status", may improve
the biological information supplied by the variables.

L39 ANSWER 11 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1998:707646 CAPLUS
DN 130:151570
TI Relationship between immunoinflammatory reactions and Alzheimer's disease
AU Du, Zeying; Li, Xiaoyu
CS Shanghai Institute of Medicine, Chinese Academy of Sciences, Shanghai,
200031, Peop. Rep. China
SO Shengli Kexue Jinzhan (1998), 29(3), 253-256
CODEN: SLKHA8; ISSN: 0559-7765
PB Zhongguo Shengli Xuehui
DT Journal; General Review
LA Chinese
AB A review with 10 refs. was reported on the relationship between
immunoinflammatory reactions and Alzheimer's disease (AD) with the
subsections as follows: (1) the pathol. characteristics of AD; (2) the
proofs of immunoinflammatory reactions; (3) the natural inhibitors in
vivo; (4) conclusions. The medicine inhibiting or blocking the
immunoinflammatory reactions in CNS may play an important role in the
prevention of AD.

L39 ANSWER 12 OF 31 MEDLINE
AN 1999090638 MEDLINE
DN 99090638
TI Measurement of pS2 protein in pancreatic cyst fluids. Evidence for a
potential role of pS2 protein in the pathogenesis of mucinous cystic
tumors .
AU Yang J M; Lee J; Southern J F; Warshaw A L; Dhanak E; Lewandrowski K B
CS Department of Pathology, Massachusetts General Hospital, Harvard Medical
School, Boston, USA.
SO INTERNATIONAL JOURNAL OF PANCREATOLOGY, (1998 Dec) 24 (3) 181-6.

Journal code: IJP. ISSN: 0169-4197.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
EW 19990504
AB CONCLUSION: Elevated levels of the growth factor pS2 protein in the cyst
fluids of mucinous cystic ***tumors*** correlate with earlier observations using immunohistochemical techniques showing that pS2 protein
is expressed by these ***tumors*** . The markedly elevated levels of
pS2 protein compared to normal plasma values suggest that this growth
factor may be important in the pathogenesis of pancreatic mucinous cystic
tumors . BACKGROUND: Cystic lesions of the pancreas include
inflammatory pseudocysts, serous cystadenomas, and mucinous cystic
tumors , some of which are malignant. Previous studies using
immunohistochemical techniques have shown that virtually all pancreatic
mucinous ***tumors*** express pS2 protein. pS2 protein is a growth
factor that is believed to be important in the normal process of
inflammation and repair. We measured pS2 protein and other growth factors
in pancreatic cyst fluids to assess their potential pathophysiologic and
diagnostic significance. METHODS: Levels of pS2 protein were measured in
54 pancreatic cyst fluids by radioimmunoassay. The growth factors,
epidermal growth factor (EGF), transforming growth factor-alpha
(TGF-alpha), and insulin-like growth factors I and II (IGF-I, IGF-II) were
measured in 22 cyst fluids using commercial immunoassays. RESULTS:
Mucinous cysts exhibited significantly higher levels of cyst fluid pS2
protein than nonmucinous lesions, including pseudocysts and serous
cystadenomas (median: 78,303 pg/mL; range: 218-361,176 pg/mL vs median:
886 pg/mL; range: 0-14,206 pg/mL; p = 0.0001). The level of pS2 in
mucinous ***tumors*** was markedly higher than plasma values (median:
392 pg/mL). Levels of pS2 protein in malignant mucinous lesions tended to
be higher than those in benign mucinous cysts, but this difference was not
statistically significant (median: 88,817 vs 64,350 pg/mL; p = 0.159).
Levels of other growth factors, including EGF, TGF-alpha, IGF-I, and
IGF-II, did not discriminate among the different cyst types, and the values were within normal plasma ranges.

L39 ANSWER 13 OF 31 MEDLINE
AN 1998249534 MEDLINE
DN 98249534
TI The pS2 protein in colorectal carcinomas and metastases.
AU Hackel C; Falkenberg B; Gunther T; Lippert H; Roessner A
CS Institute of Pathology, Otto-von-Guericke University, Magdeburg, Germany..
carsten.haeckel@medizin.uni-magdeburg.de
SO PATHOLOGY, RESEARCH AND PRACTICE, (1998) 194 (3) 171-6.
Journal code: PBZ. ISSN: 0344-0338.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199809
EW 19980901
AB Expression of pS2 protein in 50 primary ***tumors*** , metastases and
recurrent ***tumors*** of colorectal carcinomas has been analyzed by
immunohistochemistry. Sixty percent of the primary ***tumors*** were
at least focally positive for the antigen. There was no correlation
between pS2 expression and histologic grade of the lesions. In contrast,
pS2 expression in T4 and T3 ***tumors*** was significantly higher than
in T2 carcinomas. Immunoreactions in carcinomas with distant metastases
(MI) were stronger than in M0 cases. However, this difference did not
reach statistical significance. The presence of lymph node metastases did
not correlate with pS2 expression. High expression of pS2 in T4 and T3
carcinomas together with the finding of pronounced expression of the
antigen at invasion fronts in single cases could be interpreted as a
function in ***tumor*** cell invasion and motility. However, in
metastases and recurrent ***tumors*** , pS2 expression did not differ
from primary lesions (53% positive lesions). All in all, under
consideration of the latter finding in particular and together with the
randomly distributed immunopositive ***tumor*** cells and cell
clusters in the majority of cases, it is more likely that the expression
pattern of pS2 in colorectal carcinomas is a result of overall
tumor cell heterogeneity.

L39 ANSWER 14 OF 31 MEDLINE
AN 1999038014 MEDLINE
DN 99038014
TI Tamoxifen aziridine binding to cytosolic proteins from human breast
specimens is negatively associated with estrogen receptors, progesterone
receptors, pS2, and cathepsin-D.
AU Navarro D; Doreste H; Cabrera J J; Morales M; Diaz-Chico J C; Diaz-Chico B
N
CS Dept. Endocrinologia Celular y Molecular, Centro de Ciencias de la Salud,
Universidad de Las Palmas de Gran Canaria, Las Palmas, Spain.
SO BREAST CANCER RESEARCH AND TREATMENT, (1998 Jul) 50 (2) 155-66.
Journal code: A8X. ISSN: 0167-6806.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
EW 19990304
AB [3H]Tamoxifen Aziridine ([3H]TAZ) is a derivative of the antiestrogen
tamoxifen that covalently labels the Estrogen Receptor (ER), and perhaps
other uncharacterized proteins. In a previous article we described that
[3H]TAZ binds to a cytosolic protein from human uterine tissues that
shares some, but not all, the ER properties. Here we have extended these
studies to [3H]TAZ binding to cytosol proteins from human breast cancer
specimens, and studied its quantitative association with other molecular
markers and clinico-pathological variables. Cytosols were obtained in
hypotonic buffer containing 20 mM molybdate and protease inhibitors,
incubated with [3H]TAZ, and subjected to Sucrose Gradient Analysis (SGA).
A [3H]TAZ labeled peak that consistently migrated with the 4S fractions
was found in most of the assayed cytosols (range of 0 to 1278 fmol/mg
p.). The 4S peak of [3H]TAZ was partially inhibited by both estrogens and
antiestrogens. When [3H]E2 was used instead of [3H]TAZ, only an 8S peak
was detected. [3H]TAZ was covalently bound to a protein with an apparent
MW of 65 kDa, as determined by SDS-PAGE and fluorography. The mean of
[3H]TAZ binding was significantly higher in the subgroups of samples
classified as ER-, PR-, pS2- or cathepsin D-, than in the respective
positive subgroups (P < 0.01 in all the cases). [3H]TAZ binding

was not
associated with clinico-pathological variables, except that its mean was
significantly larger in ***tumors*** larger than 5 cm than in smaller
tumors . These results, and those previously reported, suggest
that: 1) [3H]TAZ labels a cytosolic protein present in human breast
cancers and uterine tissues that does not share all the ER properties, and
2) the [3H]TAZ binding by breast cancer cytosols is negatively associated
with markers of estrogenic dependency, and its quantification may provide
valuable information on antiestrogen responsiveness of a given
tumor .

L39 ANSWER 15 OF 31 MEDLINE
AN 1998409316 MEDLINE
DN 98409316
TI Direct association of ***presenilin*** -1 with beta-catenin.
AU Murayama M; Tanaka S; Palacino J; Murayama O; Honda T; Sun X; Yasutake K;
Nihonmatsu N; Wolozin B; Takashima A
CS Laboratory for Alzheimer's Disease, Brain Science Institute, RIKEN,
Saitama, Japan.
SO FEBS LETTERS, (1998 Aug 14) 433 (1-2) 73-7.
Journal code: EUH. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199812
EW 19981201
AB Families bearing mutations in the ***presenilin*** -1 (PSI) gene
develop Alzheimer's disease (AD). However, the mechanism through which PS1
causes AD is unclear. The co-immunoprecipitation with PS1 in transfected
COS-7 cells indicates that PSI directly interacts with endogenous
beta-catenin, and the interaction requires residues 322450 of PSI and
445-676 of beta-catenin. Both proteins are co-localized in the endoplasmic
reticulum. Over-expression of PS1 reduces the level of cytoplasmic
beta-catenin, and inhibits beta-catenin-T cell factor-regulated
transcription. These results indicate that PSI plays a role as inhibitor
of the beta-catenin signal, which may be connected with the AD
dysfunction.

L39 ANSWER 16 OF 31 MEDLINE
AN 1998330346 MEDLINE
DN 98330346
TI Lack of specific association of ***presenilin*** 1 (PS-1)
protein with
plaques and tangles in Alzheimer's disease.
AU Xia M Q; Berezovska O; Kim T W; Xia W M; Liao A; Tanzi R E; Selkoe D;
Hyman B T
CS Alzheimer's Research Unit, Department of Neurology, Massachusetts General
Hospital-East, Charlestown 02129, USA.
NC AG05134 (NIA)
AG08487 (NIA)
AG14744 (NIA)
SO JOURNAL OF THE NEUROLOGICAL SCIENCES, (1998 Jun 11) 158 (1) 15-23.
Journal code: JBJ. ISSN: 0022-510X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
EW 19981203
AB Missense mutations in the ***presenilin*** -1 (PS-1) gene are causally
related to the majority of familial early-onset Alzheimer's disease (FAD).
PS-1 immunohistochemical expression in normal human brain and in brains
with Alzheimer's disease (AD) has so far been controversial. Here, we
report a study of PS-1 expression in brains, cell lines and peripheral
blood mononuclear cells using a panel of well characterized PS-1-specific
antibodies. These antibodies were characterized by immunofluorescent
staining of PS-1 transfectants followed by flow cytometric analysis. In
human brain, widespread neuronal staining was observed. PS-1
immunoreactivity was primarily confined to neuronal cell bodies and
proximal dendrites. Weaker staining of microglia was also detected, in
accord with the finding of PS-1 immunoreactivity in monocytes. PS-1
expression is not particularly associated with neurons either containing
or spared from neurofibrillary tangles, nor with senile plaques. The level
of PS-1 expression does not differ between normal and AD brains.
Immunoprecipitation from AD, FAD and control brains revealed only a 32 kDa
N-terminal fragment and an 18-20 kDa C-terminal fragment. Little or no
full length PS-1 was detected. The enriched presence of PS-1 in neurons
implies an important role in neuronal function, however, the lack of
apparent association of its expression with AD pathology signifies the
need for a better understanding of its pathophysiological role.

L39 ANSWER 17 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1998:1559 CAPLUS
DN 128:73898
TI Transgenic animals expressing perlecan and amyloid genes at high levels
and methods of identifying compounds for the treatment of amyloidoses
IN Snow, Alan; Fukuchi, Ken-ichiro; Hassell, John
PA University of Washington, USA
SO PCT Int. Appl., 146 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9746664	A1	19971211	WO 97-US9875	19970606

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE,
ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR,
LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN,
ML, MR, NE, SN, TD, TG
AU 9736402 A1 19980105 AU 97-36402 19970606
PRAI US 96-17830 19960606
WO 97-US9875 19970606
AB Transgenic animals expressing a foreign gene for a perlecan, or genes for
perlecan and an amyloid are constructed for use in the testing of compds.
that can alter the rate or extent of amyloid deposition. Over-expression
of perlecan and amyloid proteins results in animals showing symptoms
closer to amyloidoses than found in animals only over-expressing an
amyloid gene, esp. Alzheimer's disease. Over-expression of a gene
encoding domains I-V of mouse perlecan and the 695-amino acid isoform of
.beta.-amyloid in P19 cells led to an up-regulation of .beta.-amyloid
synthesis and secretion. P19 cells induced to form neurons degenerated
when the perlecan gene was overexpressed.

L39 ANSWER 18 OF 31 MEDLINE DUPLICATE 2

AN 1998019211 MEDLINE
DN 98019211
TI Evidence that levels of ***presenilins*** (PS1 and PS2) are coordinately regulated by competition for limiting cellular factors.
AU Thinakaran G; Harris C L; Ratovitski T; Davenport F; Slunt H H; Price D L;
Borchelt D R; Sisodia S S
CS Department of Pathology, The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205-2196, USA..
gopal@welchlink.welch.jhu.edu
NC 1PO1 AG14248 (NIA)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Nov 7) 272 (45) 28415-22.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199802
EW 19980204
AB Mutations in two related genes, PS1 and PS2, account for the majority of
early onset cases of familial Alzheimer's disease. PS1 and PS2 are homologous polytopic membrane proteins that are processed
endoproteolytically into two fragments in vivo. In the present report we
examine the fate of endogenous PS1 and PS2 after overexpression of human
PS1 or PS2 in mouse N2a neuroblastoma cell lines and human PS1 in
transgenic mice. Remarkably, in N2a cell lines and in brains of transgenic
mice expressing human PS1, accumulation of human PS1 derivatives is
accompanied by a compensatory, and highly selective, decrease in the
steady-state levels of murine PS1 and PS2 derivatives. Similarly, the
levels of murine PS1 derivatives are diminished in cultured cells
overexpressing human PS2. To define the minimal sequence requirements for
"replacement" we expressed familial Alzheimer's disease-linked and
experimental deletion variants of PS1. These studies revealed that
compromised accumulation of murine PS1 and PS2 derivatives resulting from
overexpression of human PS1 occurs in a manner independent of
endoproteolytic cleavage. Our results are consistent with a model in which
the abundance of PS1 and PS2 fragments is regulated coordinately by
competition for limiting cellular factor(s).

L39 ANSWER 19 OF 31 MEDLINE DUPLICATE 3
AN 1998019198 MEDLINE
DN 98019198
TI Generation of anti-apoptotic ***presenilin*** -2 polypeptides by
alternative transcription, proteolysis, and caspase-3 cleavage.
AU Vito P; Ghayur T; D'Adamio L
CS T Cell Molecular Biology Unit, Laboratory of Cellular and Molecular
Immunology, NIAID, National Institutes of Health, Bethesda, Maryland
20892, USA.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Nov 7) 272 (45) 28315-20.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-U57325
EM 199802
EW 19980204
AB PS2, the chromosome 1 familial Alzheimer's disease gene, has been shown to
be involved in programmed cell death by three complementary experimental
approaches. Reduction of PS2 protein levels by antisense RNA protects from
apoptosis, whereas overexpression of an Alzheimer's PS2 mutant increases
cell death induced by several stimuli. In addition, ALG-3, a truncated PS2
cDNA, encodes an artificial COOH-terminal PS2 segment that dominantly
inhibits apoptosis. Here we describe a physiological COOH-terminal PS2
polypeptide (PS2s, Met298-Ile448) generated by both an alternative PS2
transcript and proteolytic cleavage. We find that PS2s protects
transfected cells from Fas- and ***tumor*** necrosis factor alpha
(TNFalpha)-induced apoptosis. Furthermore, a similar anti-apoptotic
COOH-terminal PS2 polypeptide (PS2Ccas) is generated by caspase-3 cleavage
at Asp329. These results suggest that caspase-3 not only activates
pro-apoptotic substrates but also generates a negative feedback signal in
which PS2Ccas antagonizes the progression of cell death. Thus, whereas PS2
is required for apoptosis, PS2s and PS2Ccas oppose this process, and the
balance between PS2 and these COOH-terminal fragments may dictate the cell
fate.

L39 ANSWER 20 OF 31 MEDLINE
AN 97450985 MEDLINE
DN 97450985
TI Endoproteolytic processing and stabilization of wild-type and mutant
presenilin .
AU Ratovitski T; Slunt H H; Thinakaran G; Price D L; Sisodia S S; Borchelt D
R
CS Division of Neuropathology, Johns Hopkins School of Medicine, Baltimore,
Maryland 21205, USA.
NC NS10580 (NINDS)
AG07914 (NIA)
AG05146 (NIA)
+
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Sep 26) 272 (39) 24536-41.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199712
EW 19971204
AB ***Presenilin*** 1 (PS1), mutated in pedigrees of early-onset familial
Alzheimer's disease, is a polytopic integral membrane protein that is
endoproteolytically cleaved into 27-kDa N-terminal and 17-kDa C-terminal
fragments. Although these fragments are the principal PS1 species found in
normal mammalian brain, the role of endoproteolysis in the maturation of
PS1 has been unclear. The present study, which uses stably transfected
mouse neuroblastoma N2a cells, demonstrates that full-length polypeptides,
derived from either wild-type or A246E FAD-mutant human (hu) PS1, are
relatively short-lived (t1/2 1.5 h) proteins that give rise to the N- and
C-terminal PS1 fragments, which are more stable (t1/2 approximately 24 h).
N-terminal fragments, generated artificially by engineering a stop codon
at amino acid 306 (PS1-306) of wild-type huPS1, were short-lived, whereas
an FAD-linked variant that lacked exon 9 (DeltaE9) and was not
endoproteolytically cleaved exhibited a long half-life. These observations
suggest that endoproteolytic cleavage and stability are not linked,
leading us to propose a model in which wild-type full-length huPS1
molecules are first stabilized then subsequently endoproteolytically
cleaved to generate the N- and C-terminal fragments. These fragments
appear to represent the mature and functional forms of wild-type huPS1.

L39 ANSWER 21 OF 31 MEDLINE
AN 97442406 MEDLINE
DN 97442406
TI Transcriptional regulation of the mouse ***presenilin*** -1 gene.
AU Mitsuda N; Roses A D; Vitek M P
CS Division of Neurology, Duke University Medical Center, Durham, North
Carolina 27710, USA.
NC RO1 AG-13839 (NIA)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Sep 19) 272 (38) 23489-97.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-AF007560
EM 199712
AB The ***presenilin*** -1 (PS-1) gene encodes at least three separate
mRNA transcripts from its 12 exons, which are spread over 50 kilobase
pairs of mouse DNA. The first transcript begins with exon 1A, whereas the
other transcripts begin with exon 1B. Different portions of exon 1B are
spliced to give long and short mRNAs. The expression of all of these
transcripts depends on a single promoter located just upstream of exon 1A.
Although this region lacks a TATA box and a number of common initiator
sequences, it does contain a CAAT box, a heat-shock responsive element, a
polyomavirus enhancer activator-3 site, an Ets 1-3 site, and multiple-Sp1
and multiple-Ap2 binding sites, which are typically found in eukaryotic
promoters. We have combined a reporter gene with various portions of this
putative PS-1 promoter and measured firefly luciferase activity relative
to an internal renilla luciferase standard. We identified a 25-base pair
fragment spanning the 5'-transcription start site of exon 1A as containing
the core of the promoter activity. The sequences downstream of this region
had undetectable promoter activity, suggesting that this core element is
the gene's only promoter, and it controls expression of all three
transcripts. Although human PS-1 mRNA expression is clearly different from
the mouse PS-1 mRNA pattern, the human and mouse core promoters do share
limited homology.

L39 ANSWER 22 OF 31 MEDLINE
AN 97268991 MEDLINE
DN 97268991
TI Endoproteolytic cleavage and proteasomal degradation of ***presenilin***
2 in transfected cells.
AU Kim T W; Pettingell W H; Hallmark O G; Moir R D; Wasco W; Tanzi R E
CS Genetics and Aging Unit, Department of Neurology, Massachusetts General
Hospital, Harvard Medical School, Charlestown, Massachusetts 02129, USA.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Apr 25) 272 (17) 11006-10.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199707
AB Mutations in the ***presenilin*** genes, PS1 and PS2, cause a major
portion of early onset familial Alzheimer's disease (FAD). The biological
roles of the ***presenilins*** and how their pathological mutations
confer FAD are unknown. In this study, we set out to examine the
processing and degradation pathways of PS2. For regulated expression of
PS2, we have established inducible cell lines expressing PS2 under the
tight control of the tetracycline-responsive transactivator. Western blot
analysis revealed that PS2 was detected as an approximately 53-55-kDa
polypeptide (54-kDa PS2) as well as a high molecular mass form (HMW-PS2).
Using a stably transfected, inducible cell system, we have found that PS2
is proteolytically cleaved into two stable cellular polypeptides including
an approximately 20-kDa C-terminal fragment and an approximately 34-kDa
N-terminal fragment. PS2 is polyubiquitinated in vivo, and the degradation
of PS2 is inhibited by proteasome inhibitors, N-acetyl-L-leucinal-L-norleucinal and lactacystin. Our studies suggest that PS2 normally
undergoes endoproteolytic cleavage and is degraded via the proteasome
pathway.

L39 ANSWER 23 OF 31 MEDLINE
AN 97289724 MEDLINE
DN 97289724
TI Evidence for phosphorylation and oligomeric assembly of ***presenilin***
1.
AU Seeger M; Nordstedt C; Petanceska S; Kovacs D M; Gouras G K; Hahne S;
Fraser P; Levesque L; Czernik A J; George-Hyslop P S; Sisodia S S;
Thinakaran G; Tanzi R E; Greengard P; Gandy S
CS Laboratory of Alzheimer Research, Department of Neurology and Neuroscience, Cornell University Medical College, New York, NY 10021, USA.
NC AG09464 (NIA)
AG11508 (NIA)
AG13780 (NIA)
+
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF
AMERICA, (1997 May 13) 94 (10) 5090-4.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199708
EW 19970801
AB Pathogenic mutations in ***presenilin*** 1 (PS1) are associated with
approximately 50% of early-onset familial Alzheimer disease. PS1 is
endoproteolytically cleaved to yield a 30-kDa N-terminal fragment (NTF)
and an 18-kDa C-terminal fragment (CTF). Using COS7 cells transfected with
human PS1, we have found that phorbol 12, 13-dibutyrate and forskolin
increase the state of phosphorylation of serine residues of the human CTF.
Phosphorylation of the human CTF resulted in a shift in electrophoretic
mobility from a single major species of 18 kDa to a doublet of 20-23 kDa.
This mobility shift was also observed with human PS1 that had been
transfected into mouse neuroblastoma (N2a) cells. Treatment of the
phosphorylated CTF doublet with phage lambda protein phosphatase
eliminated the 20- to 23-kDa doublet while enhancing the 18-kDa species,
consistent with the interpretation that the electrophoretic mobility shift
was due to the addition of phosphate to the 18-kDa species. The NTF and
CTF eluted from a gel filtration column at an estimated mass of over 100
kDa, suggesting that these fragments exist as an oligomerized species.
Upon phosphorylation of the PS1 CTF, the apparent mass of the NTF- or
CTF-containing oligomers was unchanged. Thus, the association of

PS1
fragments may be maintained during cycles of phosphorylation/dephosphoryla
tion of the PS1 CTF.

L39 ANSWER 24 OF 31 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:533425 BIOSIS
DN PREV199799832628
TI The role of ***presenilin*** -1 in the response of PC12 cells to nerve
growth factor.
AU Lah, J. J.; Bennett-Desmelik, J. A.; Heilman, C. J.; Nash, N. R.; Greenamyre, J. T.; Levey, A. I.
CS Emory Univ., Dep. Neurol., Atlanta, GA USA
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 2167.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience New
Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

L39 ANSWER 25 OF 31 MEDLINE
AN 97437409 MEDLINE
DN 97437409
TI Neuronal expression and intracellular localization of ***presenilins***
in normal and Alzheimer disease brains.
AU Huynh D P; Vinters H V; Ho D H; Ho V V; Pulst S M
CS Neurogenetics Laboratory, Burns and Allen Research Institute, Cedars-Sinai
Medical Center, Los Angeles, CA 90048, USA.
NC P30 AG 10123 (NIA)
SO JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, (1997 Sep) 56 (9)
1009-17.
Journal code: JBR. ISSN: 0022-3069.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199712
AB The expression patterns of ***presenilin*** 1 (PS1) and ***presenilin*** 2 (PS2) in human normal and Alzheimer disease (AD)
brains were investigated using antibodies to specific N-terminal peptides
of PS1 (Alzh14A and Alzh14B) and PS2 (Alzh1A-AB). The antibodies to
peptides Alzh14A (Alzh14A-AB) and Alzh14B (Alzh14B-AB) detected the
full-length protein (approximately 63 kDa) and the N-terminal-processed
fragment (36 kDa) of PS1, while the Alzh1A-AB detected mainly the
N-terminal-processed fragment (36 kDa) of PS2. Immunofluorescent staining
detected by confocal microscopy suggested that both native PS1 and PS2 are
localized mainly in the Golgi/ER apparatus. Immunohistochemical studies of
human temporal lobes from 2 normal and 5 sporadic Alzheimer brains
revealed high levels of PS1 and PS2 expression in the granule cell layer
and pyramidal neurons of the hippocampus. Strong immunoreactivity was
found in reactive astrocytes and neurofibrillary tangles of all 5
Alzheimer brains. In contrast, only 2 sporadic Alzheimer brains showed
presenilin -positive neuritic plaques. These observations suggest
that ***presenilins*** may be involved in the pathology of some cases
of sporadic AD.

L39 ANSWER 26 OF 31 MEDLINE
AN 1998063306 MEDLINE
DN 98063306
TI Determination of a cleavage site of ***presenilin*** 2 protein in
stably transfected SH-SY5Y human neuroblastoma cell lines.
AU Shirotani K; Takahashi K; Ozawa K; Kunishita T; Tabira T
CS Division of Demyelinating Disease and Aging, National Institute of
Neuroscience, Tokyo, Japan.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1997 Nov 26) 240 (3)
728-31.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199803
EW 19980303
AB Mutations in the ***presenilin*** 1 (PS1) and ***presenilin*** 2
(PS2) genes are associated with early-onset autosomal dominant familial
Alzheimer's disease, and the gene products are endoproteolytically
processed to yield N-terminal fragments (NTF) and C-terminal fragments
(CTF). We have studied the cleavage site of the PS2 protein in stably
transfected human neuroblastoma cells. The 23 kD PS2-CTF was isolated by a
combination of anion exchange chromatography and affinity chromatography
and directly sequenced. The N-terminus of the PS2-CTF started at residue
307, which indicated that the cleavage occurs between Lys306 and Leu307 in
the proximal portion of the large hydrophilic loop. This site is close to
the cleavage positions observed in the PS1 protein.

L39 ANSWER 27 OF 31 MEDLINE
AN 97474235 MEDLINE
DN 97474235
TI Alzheimer's disease-associated ***presenilin*** 1 in neuronal cells:
evidence for localization to the endoplasmic reticulum-Golgi intermediate
compartment.
AU Culvenor J G; Maher F; Evin G; Malchiodi-Albedi F; Cappai R; Underwood J
R; Davis J B; Karran E H; Roberts G W; Beyreuther K; Masters C L
CS Department of Pathology, The University of Melbourne, Parkville, Victoria,
Australia.. j.culvenor@pathology.unimelb.edu.au
SO JOURNAL OF NEUROSCIENCE RESEARCH, (1997 Sep 15) 49 (6) 719-31.
Journal code: KAC. ISSN: 0360-4012.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
AB The recently identified Alzheimer's disease-associated ***presenilin***
1 and 2 (PS1 and PS2) genes encode two homologous multi membrane-spanning
proteins. Rabbit antibodies to the N-terminal domain of PS1 detected PS1
in human neuroblastoma SH-SY5Y wild type and PS1 transfectants (SY5Y-PS1)
as well as in mouse P19, in CHO-K1 and CHO-APP770 transfected cells, in
rat cerebellar granule and hippocampal neurons, and astrocytes.
Immunoblotting detected full-length protein of 50 kDa, and a major
presumptive cleavage product of 30 kDa. The immunofluorescence pattern
resembled labeling of the endoplasmic reticulum-Golgi intermediate
compartment (ERGIC) marker protein ERGIC-53. PS1 distribution showed
slight condensation after brefeldin A and more marked condensation after
incubation of cells at 16 degrees C, characteristic of the ERGIC
compartment. Double labeling showed colocalization of ERGIC-53 with PS1 in
the SY5Y-PS1 cells. PS1 labeling of SY5Y-PS1 and P19 cells showed overlap
of the cis-Golgi marker p210 and colocalization with p210 after brefeldin
A which causes redistribution of p210 to the ERGIC. Expression of PS1 did
not change in level or cellular distribution during development of

neurons
in culture. Double labeling for the amyloid precursor protein (APP) and
PS1 on SY5Y-PS1 cells and CHO-APP770 cells showed some overlap under
control conditions. These results indicate that PS1 is a resident protein
of the ERGIC and could be involved in trafficking of proteins, including
APP, between the ER and Golgi compartments.

L39 ANSWER 28 OF 31 MEDLINE
AN 97364828 MEDLINE
DN 97364828
TI Alternative cleavage of Alzheimer-associated ***presenilins*** during
apoptosis by a caspase-3 family protease.
AU Kim T W; Pettingell W H; Jung Y K; Kovacs D M; Tanzi R E
CS Genetics and Aging Unit, Department of Neurology, Massachusetts General
Hospital, Harvard Medical School, Charlestown, MA 02129, USA.
SO SCIENCE, (1997 Jul 18) 277 (5324) 373-6.
Journal code: UJ7. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199805
EW 19980504
AB Most cases of early-onset familial Alzheimer's disease (FAD) are caused by
mutations in the genes encoding the ***presenilin*** 1 (PS1) and PS2
proteins, both of which undergo regulated endoproteolytic processing.
During apoptosis, PS1 and PS2 were shown to be cleaved at sites distal to
their normal cleavage sites by a caspase-3 family protease. In cells
expressing PS2 containing the asparagine-141 FAD mutant, the ratio of
alternative to normal PS2 cleavage fragments was increased relative to
wild-type PS2-expressing cells, suggesting a potential role for
apoptosis-associated cleavage of ***presenilins*** in the pathogenesis
of Alzheimer's disease.

L39 ANSWER 29 OF 31 MEDLINE
AN 97092711 MEDLINE
DN 97092711
TI Familial Alzheimer's disease-linked ***presenilin*** 1 variants
elevate Abeta1-42/1-40 ratio in vitro and in vivo.
AU Borchelt D R; Thinakaran G; Eckman C B; Lee M K; Davenport F; Ratovitsky
T; Prada C M; Kim G; Seekins S; Yager D; Slunt H H; Wang R; Seeger M;
Levey A I; Gandy S E; Copeland N G; Jenkins N A; Price D L; Younkin S G;
Sisodia S S
CS Department of Pathology, The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205, USA.
NC AG05146 (NIA)
NS 20471 (NINDS)
AG05689 (NIA)
+
SO NEURON, (1996 Nov) 17 (5) 1005-13.
Journal code: AN8. ISSN: 0896-6273.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199703
AB Mutations in the ***presenilin*** 1 (PS1) and ***presenilin*** 2
genes cosegregate with the majority of early-onset familial Alzheimer's
disease (FAD) pedigrees. We now document that the Abeta1-42(43)/Abeta1-40
ratio in the conditioned media of independent N2a cell lines expressing
three FAD-linked PS1 variants is uniformly elevated relative to cells
expressing similar levels of wild-type PS1. Similarly, the
Abeta1-42(43)/Abeta1-40 ratio is elevated in the brains of young
transgenic animals coexpressing a chimeric amyloid precursor protein (APP)
and an FAD-linked PS1 variant compared with brains of transgenic mice
expressing APP alone or transgenic mice coexpressing wild-type human PS1
and APP. These studies provide compelling support for the view that one
mechanism by which these mutant PS1 cause AD is by increasing the
extracellular concentration of Abeta peptides terminating at 42(43),
species that foster Abeta deposition.

L39 ANSWER 30 OF 31 MEDLINE
AN 96216717 MEDLINE
DN 96216717
TI Regional and cellular ***presenilin*** 1 gene expression in human and
rat tissues.
AU Suzuki T; Nishiyama K; Murayama S; Yamamoto A; Sato S; Kanazawa I; Sakaki
Y
CS Human Genome Center, Institute of Medical Science, University of Tokyo,
Japan.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Feb 27) 219 (3)
708-13.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199609
AB ***Presenilin*** 1 (PSNL1) is a novel causative gene for early-onset
familial Alzheimer's disease (EOFAD). We have examined the regional and
cellular distribution of PSLN1 gene expression in normal human and rat
tissues. In situ hybridization and Northern blot analysis showed that
PSNL1 mRNA was ubiquitously expressed in many different organs. We also
demonstrated that PSNL1 mRNA was expressed predominantly in the neuronal
cells of the central nervous system, but only at low-level in glial cells.
Furthermore, the distribution of PSNL1 mRNA in human and rodent brains was
similar.

L39 ANSWER 31 OF 31 MEDLINE
AN 97179560 MEDLINE
DN 97179560
TI ***Presenilin*** -1 is processed into two major cleavage products in
neuronal cell lines.
AU Ward R V; Davis J B; Gray C W; Barton A J; Bresciani L G; Caivano M;
Murphy V F; Duff K; Hutton M; Hardy J; Roberts G W; Karran E H
CS Department of Molecular Neuropathology, Smithkline Beecham Pharmaceuticals, Harlow, Essex, UK.
SO NEURODEGENERATION, (1996 Dec) 5 (4) 293-8.
Journal code: B99. ISSN: 1055-8330.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199706
EW 19970604
AB ***Presenilin*** -1 (PS-1) has been identified as the protein encoded
by the chromosome 14 locus that, when mutated, leads to familial
Alzheimer's disease (FAD). Using PS-1 transfected SHSY5Y neuroblastoma
cells, we have demonstrated by immunodetection, using polyclonal
antibodies, that PS-1 is processed to give two fragments: an N-terminal 28
kDa fragment, and a C-terminal 18 kDa fragment. In a number of
non-transfected cell types, most PS-1 is detected as the cleaved products.
The molecular weights of the PS-1 cleavage products suggest that the
cleavage point will most probably be within a region of the

hydrophilic
loop domain coded for by either exon 8 or 9 of the PS-1 gene. The clustering of FAD mutations within exon 8 strongly suggests that it encodes a key functional domain. It seems likely that the cleavage of PS-1 is crucial to some aspect of its functionality. An understanding of this process will give insights into the pathology of AD, and may offer new opportunities for therapeutic intervention.

=> s l1 and mononuclear/ab,bi

'AB' IS NOT A VALID FIELD CODE
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L40 8 L1 AND MONONUCLEAR/AB,BI

=> dup rem l40

PROCESSING COMPLETED FOR L40
L41 2 DUP REM L40 (6 DUPLICATES REMOVED)

L41 ANSWER 1 OF 2 MEDLINE DUPLICATE 1
AB Sporadic inclusion-body myositis (s-IBM) is the most common progressive muscle disease of older persons. The muscle biopsy demonstrates ***mononuclear*** cell inflammation and vacuolated muscle fibers containing paired helical filaments and 6- to 10-nm fibrils, both resembling those of Alzheimer disease brain and Congo red positivity. The term hereditary inclusion-body myopathies (h-IBMs) designates autosomal-recessive or autosomal-dominant disorders with muscle biopsies cytopathologically similar to s-IBM but without inflammation. Vacuolated muscle fibers of both s-IBM and the h-IBMs contain accumulations of several "Alzheimer-characteristic proteins" including beta-amyloid protein and beta-amyloid precursor protein, and their paired helical filaments are composed of phosphorylated tau. We used six well characterized antibodies against several residues of ***presenilin*** 1 (PS1) to immunostain muscle biopsies of 12 patients with s-IBM, 5 patients with autosomal-recessive inclusion-body myopathy, and 16 normal and disease controls. Seventy to eighty percent of the vacuolated muscle fibers of both s-IBM and autosomal-recessive inclusion-body myopathy had inclusions that were strongly PS1-immunoreactive, which by immunoelectron microscopy localized mainly to paired helical filaments and 6- to 10-nm filaments. None of the control biopsies had PS1-positive inclusions characteristic of the s- and h-IBM abnormal muscle fibers. Mutations of the newly discovered PS1 gene are responsible for early-onset familial Alzheimer disease (AD), and PS1 is abnormally accumulated in sporadic and familial AD brain. Our study provides the first demonstration of PS1 abnormality in non-neural tissue and in diseases other than AD and suggests that the cytopathogenesis in AD brain and IBM muscle may share similarities.

L41 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
AB Missense mutations in the ***presenilin*** -1 (PS-1) gene are causally related to the majority of familial early-onset Alzheimer's disease (FAD). PS-1 immunohistochemical expression in normal human brain and in brains with Alzheimer's disease (AD) has so far been controversial. Here, we report a study of PS-1 expression in brains, cell lines and peripheral blood ***mononuclear*** cells using a panel of well characterized PS-1-specific antibodies. These antibodies were characterized by immunofluorescent staining of PS-1 transfectants followed by flow cytometric analysis. In human brain, widespread neuronal staining was observed. PS-1 immunoreactivity was primarily confined to neuronal cell bodies and proximal dendrites. Weaker staining of microglia was also detected, in accord with the finding of PS-1 immunoreactivity in monocytes. PS-1 expression is not particularly associated with neurons either containing or spared from neurofibrillary tangles, nor with senile plaques. The level of PS-1 expression does not differ between normal and AD brains. Immunoprecipitation from AD, FAD and control brains revealed only a 32 kDa N-terminal fragment and an 18-20 kDa C-terminal fragment. Little or no full length PS-1 was detected. The enriched presence of PS-1 in neurons implies an important role in neuronal function, however, the lack of apparent association of its expression with AD pathology signifies the need for a better understanding of its pathophysiological role.

=> d 1- bib ab

YOU HAVE REQUESTED DATA FROM 2 ANSWERS - CONTINUE? Y/(N):y

L41 ANSWER 1 OF 2 MEDLINE DUPLICATE 1
AN 1998206425 MEDLINE
DN 98206425
TI Light and electron microscopic immunolocalization of ***presenilin*** 1 in abnormal muscle fibers of patients with sporadic inclusion-body myositis and autosomal-recessive inclusion-body myopathy.
AU Askanas V; Engel W K; Yang C C; Alvarez R B; Lee V M; Wisniewski T
CS USC Neuromuscular Center, Los Angeles, California 90017-1912, USA.
SO AMERICAN JOURNAL OF PATHOLOGY, (1998 Apr) 152 (4) 889-95.
Journal code: 3RS. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199807
EW 19980701
AB Sporadic inclusion-body myositis (s-IBM) is the most common progressive muscle disease of older persons. The muscle biopsy demonstrates ***mononuclear*** cell inflammation and vacuolated muscle fibers containing paired helical filaments and 6- to 10-nm fibrils, both resembling those of Alzheimer disease brain and Congo red positivity. The term hereditary inclusion-body myopathies (h-IBMs) designates autosomal-recessive or autosomal-dominant disorders with muscle biopsies cytopathologically similar to s-IBM but without inflammation. Vacuolated muscle fibers of both s-IBM and the h-IBMs contain accumulations of several "Alzheimer-characteristic proteins" including beta-amyloid protein and beta-amyloid precursor protein, and their paired helical filaments are composed of phosphorylated tau. We used six well characterized antibodies against several residues of ***presenilin*** 1 (PS1) to immunostain muscle biopsies of 12 patients with s-IBM, 5 patients with autosomal-recessive inclusion-body myopathy, and 16 normal and disease controls. Seventy to eighty percent of the vacuolated muscle fibers of both s-IBM and autosomal-recessive inclusion-body myopathy had

inclusions
that were strongly PS1-immunoreactive, which by immunoelectron microscopy
localized mainly to paired helical filaments and 6- to 10-nm filaments.
None of the control biopsies had PS1-positive inclusions characteristic of
the s- and h-IBM abnormal muscle fibers. Mutations of the newly discovered
PS1 gene are responsible for early-onset familial Alzheimer disease (AD),
and PS1 is abnormally accumulated in sporadic and familial AD brain. Our
study provides the first demonstration of PS1 abnormality in non-neural
tissue and in diseases other than AD and suggests that the
cytopathogenesis in AD brain and IBM muscle may share similarities.

L41 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
AN 1998330346 MEDLINE
DN 98330346
TI Lack of specific association of ***presenilin*** 1 (PS-1) protein with
plaques and tangles in Alzheimer's disease.
AU Xia M Q; Berezovska O; Kim T W; Xia W M; Liao A; Tanzi R E; Selkoe D;
Hyman B T
CS Alzheimer's Research Unit, Department of Neurology, Massachusetts General
Hospital-East, Charlestown 02129, USA.
NC AG05134 (NIA)
AG08487 (NIA)
AG14744 (NIA)
SO JOURNAL OF THE NEUROLOGICAL SCIENCES, (1998 Jun 11) 158 (1) 15-23.
Journal code: JBJ. ISSN: 0022-510X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
EW 19981203
AB Missense mutations in the ***presenilin*** -1 (PS-1) gene are causally
related to the majority of familial early-onset Alzheimer's disease (FAD).
PS-1 immunohistochemical expression in normal human brain and in brains
with Alzheimer's disease (AD) has so far been controversial. Here, we
report a study of PS-1 expression in brains, cell lines and peripheral
blood ***mononuclear*** cells using a panel of well characterized
PS-1-specific antibodies. These antibodies were characterized by
immunofluorescent staining of PS-1 transfectants followed by flow
cytometric analysis. In human brain, widespread neuronal staining was
observed. PS-1 immunoreactivity was primarily confined to neuronal cell
bodies and proximal dendrites. Weaker staining of microglia was also
detected, in accord with the finding of PS-1 immunoreactivity in
monocytes. PS-1 expression is not particularly associated with neurons
either containing or spared from neurofibrillary tangles, nor with senile
plaques. The level of PS-1 expression does not differ between normal and
AD brains. Immunoprecipitation from AD, FAD and control brains revealed
only a 32 kDa N-terminal fragment and an 18-20 kDa C-terminal fragment.
Little or no full length PS-1 was detected. The enriched presence of PS-1
in neurons implies an important role in neuronal function, however, the
lack of apparent association of its expression with AD pathology signifies
the need for a better understanding of its pathophysiological role.

=> s l1 and endothelial/ab,bi

'AB' IS NOT A VALID FIELD CODE
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'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
L42 10 L1 AND ENDOTHELIAL/AB,BI

=> dup rem l42

PROCESSING COMPLETED FOR L42
L43 4 DUP REM L42 (6 DUPLICATES REMOVED)

=> d 1- bib ab

YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):y

L43 ANSWER 1 OF 4 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:471358 BIOSIS
DN PREV199799770561
TI ***Presenilin*** 1 is involved in cerebral amyloid angiopathy of
Alzheimer's disease affected brains.
AU Hayashi, Y. (1); Fukatsu, R.; Tsuzuki, K.; Yoshida, T.; Takamaru, Y.;
Sasaki, N.; Yamaguchi, H.; Fujii, N.; Takahata, N.
CS (1) Dep. Neuropsychiatry, Sapporo Med. Univ., South 1, West 16, Chuo-ku,
Sapporo 060 Japan
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 825.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1
New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

L43 ANSWER 2 OF 4 MEDLINE DUPLICATE 1
AN 97404082 MEDLINE
DN 97404082
TI Superoxide free radical and intracellular calcium mediate A beta(1-42)
induced ***endothelial*** toxicity.
AU Suo Z; Fang C; Crawford F; Mullan M
CS Department of Psychiatry, University of South Florida, Tampa 33613, USA.
SO BRAIN RESEARCH, (1997 Jul 11) 762 (1-2) 144-52.
Journal code: B5L. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199712
EW 19971201
AB The 39-42 amino acid residue amyloid beta peptide (A beta), the major
protein component in senile plaques and cerebrovascular amyloidosis in the
brain in Alzheimer's disease (AD), has been shown to be neurotoxic in
vitro. Accumulating data from several areas suggest that cerebrovascular
dysfunction and damage may also play a significant role in the AD process.
For instance, we have recently demonstrated enhanced vasoconstriction and
resistance to relaxation in intact rat aorta treated with A beta [Thomas
et al., beta-Amyloid-mediated vasoactivity and vascular ***endothelial*** damage, Nature, 380 (1996) 168-171]. Significant
vessel damage occurred after thirty minutes of exposure, but could be
prevented with superoxide dismutase. To further investigate the role of A
beta toxicity on ***endothelial*** cells, we have applied A beta
peptides to cultures of human aortic ***endothelial*** cells (HAEC).
Our results show that both A beta(1-42) and A beta(25-35) are toxic to
HAEC in a time- and dose-dependent manner, and that this toxicity can be
partially prevented by the calcium channel blocker, verapamil, and the
antioxidant, superoxide dismutase. The common form of A beta, A beta(1-40), which has been shown to be neurotoxic, is much less toxic to

HAEC. A beta toxicity to HAEC occurs within 30 min of treatment with relatively lower doses than those usually observed in primary cultured neurons and vascular smooth muscle cells. It was recently reported that a variety of mutations in the beta-amyloid protein precursor gene and the ***Presenilin*** -1 and -2 genes linked to early-onset familial AD cause an increase in the plasma concentration of A beta(1-42) in mutation carriers [Scheuner et al., Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vitro by the ***presenilin*** 1 and 2 and APP mutations linked to familial Alzheimer's disease, Nature Med., 2 (1996) 864-870]. Human aortic ***endothelial*** cells are more sensitive to A beta(1-42) than A beta(1-40), via a pathway involving an excess of superoxide free radicals and influx of extracellular calcium. Finally, we have evidence that both apoptotic and necrotic processes are activated by the A beta peptides in these ***endothelial*** cells.

L43 ANSWER 3 OF 4 CAPLUS COPYRIGHT 1999 ACS
AN 1998:109324 CAPLUS
DN 128:163691
TI Central role of oxyradicals in the mechanism of amyloid b-peptide cytotoxicity
AU Mattson, Mark P.
CS Sanders-Brown Res. Cent. on Aging and Dep. Anatomy & Neurobiol., Univ. Kentucky, Lexington, KY, 40636-0230, USA
SO Alzheimer's Dis. Rev. (1997), 2(1/2), 1-14
CODEN: ADREFN
URL: http://www.coa.uky.edu/ADReview/Mattson.htm
PB Sanders-Brown Center on Aging, University of Kentucky
DT Journal; General Review; (online computer file)
LA English
AB A review and discussion with many refs. Overwhelming evidence indicates that cells in Alzheimer's disease brain are subjected to abnormally high levels of oxidative stress, and that amyloids are a focus of cellular and mol. oxidn. Recent studies suggest that amyloid b-peptide (Ab) plays a major role in promoting oxidative stress in neurons and glial cells, and that such oxidative stress can account for many of the metabolic and neurodegenerative alterations obsd. in AD brain. Ab induces membrane lipid peroxidn. in neurons which leads to impairment of ion-motive ATPases, and glutamate and glucose transporters. These actions of Ab lead to membrane depolarization and energy failure which, in turn, promote excitotoxic and apoptotic degenerative depolarization and energy failure which, in turn, promote excitotoxic and apoptotic degenerative cascades involving calcium overload. Membrane oxidn., as induced by Ab, also disrupts coupling of metabotropic receptors to their GTP-binding proteins, which may account for the well-known cholinergic signaling deficits and assocd. cognitive impairment in AD. 4-Hydroxynonenal, an aldehydic prodn. of membrane lipid peroxidn., is implicated as a mediator of Ab-induced disruption of cellular ion and energy homeostasis, and neuronal apoptosis. Oxidative stress induced by Ab in microglia and astrocytes likely contributes to the inflammatory process in AD brain. Moreover, Ab-mediated oxidative damage to vascular ***endothelial*** cells may contribute to the impaired glucose transport and compromised barrier function of the cerebral vessels in AD. Finally, the possible mechanistic links between mutations in ***presenilin*** genes, oxidative stress, and neuronal degeneration in AD are considered.

L43 ANSWER 4 OF 4 MEDLINE DUPLICATE 2
AN 96234265 MEDLINE
DN 96234265
TI Widespread neuronal expression of the ***presenilin*** -1 early-onset Alzheimer's disease gene in the murine brain.
AU Cribbs D H; Chen L S; Bende S M; LaFerla F M
CS Department of Neurology, University of California, Irvine, USA.
NC P50-AG01542 (NIA)
SO AMERICAN JOURNAL OF PATHOLOGY, (1996 Jun) 148 (6) 1797-806.
Journal code: 3RS. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199610
AB Mutations in the ***presenilin*** -1 (S182) gene have been genetically linked to early-onset Alzheimer's disease. To clarify the underlying molecular mechanism through which ***presenilin*** -1 is involved in the pathogenesis of this neurodegenerative disorder, the regional and cellular transcription profile of this gene was characterized in primary cells isolated from the murine brain by Northern blot hybridization using digoxigenin-labeled riboprobes. Our results indicate that ***presenilin*** -1 mRNA transcripts are widely distributed throughout the adult mouse brain. Furthermore, immunohistochemical labeling of hybridized sections indicates that expression was predominantly localized to neuronal cells. Neurons in the hippocampus and cerebral cortex, which are severely compromised in Alzheimer's disease, showed prominent expression of ***presenilin*** -1. In contrast, white matter areas and ***endothelial*** cells do not appear to express ***presenilin*** -1 to detectable levels. ***presenilin*** -1 transcripts, however, are also present less frequently in certain nonneuronal cell populations such as ependymal cells in the choroid plexus. Analysis of primary cells isolated from murine brain supported the results obtained by in situ hybridization and showed that cultured primary neurons and astrocytes express ***presenilin*** -1. Overall, it appears that the pattern of ***presenilin*** -1 gene expression parallels that previously described for the amyloid precursor protein.

=> s l1 and astrocyte#/ab,bi

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'AB' IS NOT A VALID FIELD CODE
L44 61 L1 AND ASTROCYTE#/AB,BI

=> dup rem l44

PROCESSING COMPLETED FOR L44
L45 26 DUP REM L44 (35 DUPLICATES REMOVED)

=> s l44 and presenilin-2/ab,bi

'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
L46 27 L44 AND PRESENILIN-2/AB,BI

=> dup rem l46

PROCESSING COMPLETED FOR L46

L47 13 DUP REM L46 (14 DUPLICATES REMOVED)

=> d l- bib ab

YOU HAVE REQUESTED DATA FROM 13 ANSWERS - CONTINUE? Y/(N):y

L47 ANSWER 1 OF 13 MEDLINE DUPLICATE 1
AN 1998099802 MEDLINE
DN 98099802
TI Interaction of ***presenilins*** with the filamin family of actin-binding proteins.
AU Zhang W; Han S W; McKeel D W; Goate A; Wu J Y
CS Department of Pediatrics and Molecular Biology and Pharmacology, Washington University School of Medicine, St. Louis, Missouri 63110, USA.
NC AG-05861 (NIA)
AG00634 (NIA)
AG05681 (NIA)
SO JOURNAL OF NEUROSCIENCE, (1998 Feb 1) 18 (3) 914-22.
Journal code: JDF. ISSN: 0270-6474.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199804
EW 19980402
AB Mutations in ***presenilin*** genes PS1 and PS2 account for approximately 50% of early-onset familial Alzheimer's disease (FAD). The PS1 and PS2 genes encode highly homologous transmembrane proteins related to the Caenorhabditis elegans sel-12 and spe-4 gene products. A hydrophilic loop region facing the cytoplasmic compartment is likely to be functionally important because at least 14 mutations in FAD patients have been identified in this region. We report here that the loop regions of PS1 and PS2 interact with nonmuscle filamin (actin-binding protein 280, ABP280) and a structurally related protein (filamin homolog 1, Fh1). Overexpression of PS1 appears to modify the distribution of ABP280 and Fh1 proteins in cultured cells. A monoclonal antibody recognizing ABP280 and Fh1 binds to blood vessels, ***astrocytes*** , neurofibrillary tangles, neuropil threads, and dystrophic neurites in the AD brain. Detection of ABP280/Fh1 proteins in these structures suggests that these ***presenilin*** -interacting proteins may be involved in the development of AD and that interactions between ***presenilins*** and ABP280/Fh1 may be functionally significant. The ABP280 gene is located on the human X chromosome, whereas the newly identified Fh1 gene maps to human chromosome 3. These results provide a new basis for understanding the function of ***presenilin*** proteins and further implicate cytoskeletal elements in AD pathogenesis.

L47 ANSWER 2 OF 13 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1999:52671 BIOSIS
DN PREV199900052671
TI Double transgenic mice carrying mutant amyloid beta precursor protein and ***presenilin*** 1 genes express accelerated Alzheimer-like phenotype.
AU Sugaya, K. (1); Jerome, S. (1); Bryan, D.; McKinney, M.; Duff, K.; Kumar, V. (1)
CS (1) Westside VA Med. Cent., Chicago, IL 60612 USA
SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 728.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1
Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience
. ISSN: 0190-5295.
DT Conference
LA English

L47 ANSWER 3 OF 13 MEDLINE DUPLICATE 2
AN 1998267265 MEDLINE
DN 98267265
TI Cloning and characterization of the ***presenilin*** - ***2*** gene promoter.
AU Pennypacker K R; Fuldner R; Xu R; Hernandez H; Dawbarn D; Mehta N; Perez-Tur J; Baker M; Hutton M
CS Department of Pharmacology and Therapeutics, University of South Florida, Tampa, FL 33612, USA.
NC AG14633 (NIA)
SO BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1998 May) 56 (1-2) 57-65.
Journal code: MBR. ISSN: 0169-328X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
EW 19990303
AB Mutations in the ***presenilin*** - ***2*** (PS-2) have been shown to cause early onset Alzheimer's disease (AD) in a series of families known as the Volga Germans and in an unrelated Italian kindred. Expression of the PS-2 gene is regulated during AD, aging, development and brain injury. Although expressed primarily in neurons, enhanced levels of PS-2 have been reported in ***astrocytes*** activated by neuronal damage. Understanding the regulation of the PS-2 gene may thus provide an insight into its role in AD. We have isolated a 3635 bp DNA fragment that contains 2934 bp of DNA sequence upstream from the PS-2 gene. Primer extension analysis was used to map three major transcriptional start sites within the PS-2 gene. The promoter sequence, upstream of each transcriptional start site, does not contain TATA or CAAT boxes but does contain several GC rich sites (Sp-1 and AP-2). A reporter gene construct containing the PS-2 promoter (PS2P, -2934 to +702) transfected into M17 cells drives basal transcription to 20% of the levels of the SV-40 viral promoter. Addition of NGF to PC-12 cells was found to upregulate the PS2P promoter and an NGF-responsive element was localized by deletional analysis between -403 and +13 within the promoter. Since the PS-2 gene has multiple start sites and the upstream sequence is GC rich with no TATA box, the PS-2 promoter is consistent with the GC class of 'housekeeping' genes.
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L47 ANSWER 4 OF 13 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1999:32125 BIOSIS
DN PREV199900032125
TI Endogenous ***presenilin*** : 1. ***Presenilin*** ***2*** and soluble APP in primary cultures of fetal rat ***astrocytes*** and neurons: Effects of 5-HT2A/C, adenylyl cyclase, or PGE2 stimulation on normal, alternative and novel proteolytic fragments.
AU Paradis, M. D.; Lee, R. K.; Wurtman, R. J.
CS Dep. Brain Cognitive Sci., MIT, Cambridge, MA 02139 USA
SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 6.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1
Los Angeles, California, USA November 7-12, 1998 Society for

Neuroscience
. ISSN: 0190-5295.
DT Conference
LA English

L47 ANSWER 5 OF 13 MEDLINE DUPLICATE 3
AN 1998041524 MEDLINE
DN 98041524
TI Cellular expression and proteolytic processing of ***presenilin***
proteins is developmentally regulated during neuronal differentiation.
AU Capell A; Saffrich R; Olivo J C; Meyn L; Walter J; Grunberg J; Mathews P;
Nixon R; Dotti C; Haass C
CS Central Institute of Mental Health, Department of Molecular Biology,
Mannheim, Germany.
SO JOURNAL OF NEUROCHEMISTRY, (1997 Dec) 69 (6) 2432-40.
Journal code: JAV. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
EW 19980204
AB We have determined the expression of the Alzheimer's disease-associated
proteins ***presenilin*** -1 and ***presenilin*** - ***2*** in
primary cultures of rat hippocampal neurons. Neurons highly express
presenilin -1 and ***presenilin*** - ***2*** , whereas both
proteins were not detected in ***astrocytes*** . Further, we have
analyzed the subcellular localization and expression in rat hippocampal
neurons during development. Although ***presenilin*** proteins were
localized predominantly to the endoplasmic reticulum in nonneuronal cells
transfected with ***presenilin*** cDNAs, in neurons,
presenilin proteins were also found in compartments not staining
with antibodies to grp78(BiP). ***Presenilin*** -1 and
presenilin - ***2*** were predominantly detected in vesicular
structures within the somatodendritic compartment with much less
expression in axons. Polarized distribution of ***presenilin*** -1 and
presenilin - ***2*** differs slightly, with more
presenilin - ***2*** expressed in axons compared with
presenilin -1. ***Presenilin*** expression was found to be
developmentally regulated. ***Presenilin*** expression strongly
increased during neuronal differentiation until full morphological
polarization and then declined. No full-length ***presenilin*** -1 or
presenilin - ***2*** could be detected within cell lysates. At
early developmental stages the expected approximately 34-kDa N-terminal
proteolytic fragment of ***presenilin*** -1 and the approximately
38-kDa fragment of ***presenilin*** - ***2*** were detected. Later
during differentiation we predominantly detected a approximately 38-kDa
fragment for ***presenilin*** -1 and a approximately 42-kDa fragment
for ***presenilin*** - ***2*** . By epitope mapping, we show that
these slower migrating peptides represent N-terminal proteolytic
fragments, cleaved C-terminal to the conventional site of processing. It
is noteworthy that both ***presenilin*** -1 and ***presenilin*** -
2 undergo alternative proteolytic cleavage at the same stage of
neuronal differentiation. Regulation of ***presenilin*** expression
and proteolytic processing might have implications for the pathological as
well as the biological function of ***presenilins*** during aging in
the human brain.

L47 ANSWER 6 OF 13 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:425474 BIOSIS
DN PREV199799724677
TI ***Presenilin*** 1 (S182) and 2 (STM2) mRNA and protein in sporadic
Alzheimer's disease (AD.
AU Stopa, E. G. (1); Taylor, W. (1); Rubin, B. S.; Roses, A. D.; Schmechel,
D.; Kuo-Leblanc, V. (1); Wei, Y.; Song, P. C. (1); King, J. C.; Boteva,
K.; Mitsuda, N.; Gilbert, J. R.; Vitek, M. P.
CS (1) Brown Univ., Providence, RI USA
SO Brain Pathology, (1997) Vol. 7, No. 4, pp. 1204.
Meeting Info.: XIIIth International Congress of Neuropathology Perth,
Western Australia, Australia September 7, 1997
ISSN: 1015-6305.
DT Conference; Abstract; Conference
LA English

L47 ANSWER 7 OF 13 MEDLINE DUPLICATE 4
AN 97437409 MEDLINE
DN 97437409
TI Neuronal expression and intracellular localization of ***presenilins***
in normal and Alzheimer disease brains.
AU Huynh D P; Vinters H V; Ho D H; Ho V V; Pulst S M
CS Neurogenetics Laboratory, Burns and Allen Research Institute, Cedars-Sinai
Medical Center, Los Angeles, CA 90048, USA.
NC P30 AG 10123 (NIA)
SO JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, (1997 Sep) 56 (9)
1009-17.
Journal code: JBR. ISSN: 0022-3069.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199712
AB The expression patterns of ***presenilin*** 1 (PS1) and
presenilin ***2*** (PS2) in human normal and Alzheimer disease
(AD) brains were investigated using antibodies to specific N-terminal
peptides of PS1 (Alzh14A and Alzh14B) and PS2 (Alzh1A-AB). The antibodies
to peptides Alzh14A (Alzh14A-AB) and Alzh14B (Alzh14B-AB) detected the
full-length protein (approximately 63 kDa) and the N-terminal-processed
fragment (36 kDa) of PS1, while the Alzh1A-AB detected mainly the
N-terminal-processed fragment (36 kDa) of PS2. Immunofluorescent staining
detected by confocal microscopy suggested that both native PS1 and PS2 are
localized mainly in the Golgi/ER apparatus. Immunohistochemical studies of
human temporal lobes from 2 normal and 5 sporadic Alzheimer brains
revealed high levels of PS1 and PS2 expression in the granule cell layer
and pyramidal neurons of the hippocampus. Strong immunoreactivity was
found in reactive ***astrocytes*** and neurofibrillary tangles of all
5 Alzheimer brains. In contrast, only 2 sporadic Alzheimer brains showed
presenilin -positive neuritic plaques. These observations suggest
that ***presenilins*** may be involved in the pathology of some cases
of sporadic AD.

L47 ANSWER 8 OF 13 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:471357 BIOSIS
DN PREV199799770560

TI ***Presenilin*** -1 is closely related with neurofibrillary tangles in
the Alzheimer's brain.
AU Tomidokoro, Y.; Ishiguro, K.; Igeta, Y.; Shizuka, M.; Kawarabayashi, T.;
Matsubara, E.; Kanai, M.; Harigaya, Y.; Okamoto, K.; Shoji, M.
CS Dep. Neurol., Gumma Univ. Sch. Med., 3-39-15 Showa-machi, Maebashi, Gunma
371 Japan
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 825.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1
New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

L47 ANSWER 9 OF 13 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:517865 BIOSIS
DN PREV199799817068
TI Amyotrophic lateral sclerosis and Alzheimer's disease. Lessons from model
systems.
AU Price, D. L. (1); Wong, P. C.; Borchelt, D. R.; Pardo, C. A.; Thinakaran,
G.; Doan, A. P.; Lee, M. K.; Martin, L. J.; Sisodia, S. S.
CS (1) Neuropathol. Lab., Johns Hopkins Univ. Sch. Med., 558 Ross Research
Bldg., 720 Rutland Ave., Baltimore, MD 21205-2196 USA
SO Revue Neurologique (Paris), (1997) Vol. 153, No. 8-9, pp. 484-495.
ISSN: 0035-3787.
DT General Review
LA English
SL English; French
AB The human neurodegenerative diseases, including motor neuron disease and
Alzheimer's disease (AD), are characterized by a selective involvement of
certain regions of the brain/spinal cord and of selected populations of
neurons. Sporadic amyotrophic lateral sclerosis (ALS) is an age-associated
disease with cytoskeletal abnormalities and death of motor neurons;
familial ALS (FALS), an autosomal dominant disease linked to mutations in
superoxide dismutase 1 (SOD1), is manifested by inclusions and
degeneration of motor neurons. Autosomal dominant familial AD (FAD),
linked to mutations in ***presenilin*** (PS1 and PS2) genes or the
amyloid precursor protein (APP) gene, shows brain abnormalities (e.g.,
neurofibrillary tangles, deposits of cntdot -amyloid A cntdot , and death
of subsets of neurons) similar to those that occur in sporadic AD, the
risk of which is enhanced by the presence of one or two copies of
apolipoprotein E4 (apoE4) alleles. To examine the mechanisms of these
diseases, investigators have used a variety of animal models, including
experimentally produced, spontaneously occurring, or genetically
engineered models of disease. Studies of models of degeneration of motor
neurons (axotomy) and cytoskeletal abnormalities seen in motor neuron
disease (i.e., axonopathy induced by cntdot , cntdot '-
iminodipropionitrile (IDPN), hereditary canine spinal muscular atrophy
(HCSMA), and neurofilament NF transgenic Tg mice) have demonstrated that
NF-filled swellings of axons are related to alterations in the biology of
NF transport. Tg mice with SOD1 mutations, which develop the clinical
features of FALS, show selective degeneration of motor neurons, which is
attributed to the acquisition of toxic properties by mutant SOD1. Models
of AD include: aged monkeys that show both cognitive/memory deficits and
cellular abnormalities (amyloid deposition/cytoskeletal abnormalities of
neurons) in cortex and hippocampus; and Tg mice that express mutant human
FAD-linked genes (i.e., APP and PS1) and show increased levels of A-42,
amyloid deposits, dystrophic neurites, and local responses of
astrocytes and microglia. This review discusses the
behavioral/neuropathological features of AD, the results of investigations
of the mechanisms of disease in model systems, and the potential utility
of some of these models for testing new therapies.

L47 ANSWER 10 OF 13 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:468096 BIOSIS
DN PREV199799767299
TI Expression of Alzheimer's disease related genes in three human astrocytic
cell lines.
AU Shepherd, C. E.; Calvert, E. L.; Cambray-Deakin, M. A.; Pearson, R. C. A.
CS Dep. Biomedical Sci., Univ. Sheffield, S10 2TN UK
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 266.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1
New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

L47 ANSWER 11 OF 13 MEDLINE DUPLICATE 5
AN 97220077 MEDLINE
DN 97220077
TI Expression of ***presenilin*** -1 and -2 mRNAs in rat and Alzheimer's
disease brains.
AU Takami K; Terai K; Matsuo A; Walker D G; McGeer P L
CS Pharmaceutical Development Division, Takeda Chemical Industries, Ltd.,
Osaka, Japan.
SO BRAIN RESEARCH, (1997 Feb 14) 748 (1-2) 122-30.
Journal code: B5L. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
AB Recently, new genetic linkages have been identified for early-onset
familial Alzheimer's disease (AD). Mutations have been found in the
presenilin (PS)-1 (S182) gene on chromosome 14 and the PS-2
(STM2/E5-a) gene on chromosome 1. We have investigated the distribution of
gene expression of both ***presenilins*** in normal rat brain, and in
human control and AD cases using in situ hybridization histochemistry. In
normal rat brain, intense PS-1 mRNA expression was observed predominantly
in neurons, particularly hippocampal pyramidal and dentate granular
neurons and cerebellar Purkinje and granular neurons. The distribution of
intensely expressing PS-2 mRNA cells was similar to that of PS-1, but
additional groups in the brain stem and cortex were identified. Faint but
significant mRNA expression of both PS genes was detected in white matter.
In control human cases, the same neuronal cell types as seen in rat brain
expressed both PS mRNAs in the hippocampus and cerebellum. In AD cases,
the expression of both mRNAs was markedly decreased in the hippocampus but
not in the cerebellum. In addition, PS-2 hybridization showed increased
mRNA expression in ***astrocyte*** -like cells in affected areas of AD
cases. The present data indicate that the PS genes may play important
roles in specific neurons in normal brain, and that the decreased
expression in neurons in sporadic AD brain may bear some relationship to

the pathogenesis.

L47 ANSWER 12 OF 13 CAPLUS COPYRIGHT 1999 ACS
AN 1997:227178 CAPLUS
DN 126:275585
TI Familial Alzheimer disease gene: ***presenilin*** 1 and 2
AU Tabira, Takeshi
CS Natl. Inst. Neuroscience, Tokyo, 187, Japan
SO Shinkei Kenkyu no Shinpo (1997), 41(1), 8-17
CODEN: SKNSAF; ISSN: 0001-8724
PB Igaku Shoin
DT Journal; General Review
LA Japanese
AB A review, with 50 refs. Since the discovery of ***presenilin*** 1 (PS1) and ***presenilin*** ***2*** (PS2) genes, about 2 yr has passed. Over 30 point mutations in PS1 gene were found in early onset familial Alzheimer's disease families in the world, and a mutation of PS2 was found in the Volga-German family. However, in our studies, PS1 mutations were found in less than 20% of Japanese families of Alzheimer's disease, and none was shown to have mutations in PS2. Therefore, important causative or risk factor genes are still missing. PS1 and PS2 genes are very homologous, and numerous isoforms are produced by alternative splicing. The full length protein of PS1 is 47 kDa protein and it is supposed to function after cleavage into two fragments. Both PS1 and PS2 are expressed mainly in Golgi and ER of neurons, but a part of ***astrocytes*** that surround vessels and senile plaques also contain this substance. It is still immature to know the function of PS1 and PS2, and the pathomechanism of Alzheimer's disease due to mutations of these genes is still unknown.

L47 ANSWER 13 OF 13 MEDLINE DUPLICATE 6
AN 97081125 MEDLINE
DN 97081125
TI Expression of ***presenilin*** 1 and 2 (PS1 and PS2) in human and murine tissues.
AU Lee M K; Slunt H H; Martin L J; Thinakaran G; Kim G; Gandy S E; Seeger M; Koo E; Price D L; Sisodia S S
CS Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.
NC AG05146 (NIA)
NS20471 (NINDS)
SO JOURNAL OF NEUROSCIENCE, (1996 Dec 1) 16 (23) 7513-25.
Journal code: JDF. ISSN: 0270-6474.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199703
EW 19970302
AB Mutations in genes encoding related proteins, termed ***presenilin*** 1 (PS1) and ***presenilin*** ***2*** (PS2), are linked to the majority of cases with early-onset familial Alzheimer's disease (FAD). To clarify potential function(s) of ***presenilins*** and relationships of ***presenilin*** expression to pathogenesis of AD, we examined the expression of PS1 and PS2 mRNA and PS1 protein in human and mouse. Semi-quantitative PCR of reverse-transcribed RNA (RT-PCR) analysis revealed that PS1 and PS2 mRNA are expressed ubiquitously and at comparable levels in most human and mouse tissues, including adult brain. However, PS1 mRNA is expressed at significantly higher levels in developing brain. In situ hybridization studies of mouse embryos revealed widespread expression of PS1 mRNA with a neural expression pattern that, in part, overlaps that reported for mRNA encoding specific Notch homologs. In situ hybridization analysis in adult mouse brain revealed that PS1 and PS2 mRNAs are enriched in neurons of the hippocampal formation and entorhinal cortex. Although PS1 and PS2 mRNA are expressed most prominently in neurons, lower but significant levels of PS1 and PS2 transcripts are also detected in white matter glial cells. Moreover, cultured neurons and ***astrocytes*** express PS1 and PS2 mRNAs. Using PS1-specific antibodies in immunoblot analysis, we demonstrate that PS1 accumulates as approximately 28 kDa N-terminal and approximately 18 kDa C-terminal fragments in brain. Immunocytochemical studies of mouse brain reveal that PS1 protein accumulates in a variety of neuronal populations with enrichment in somatodendritic and neuropil compartments.

=> s l1 and microglia#/ab,bi
'AB' IS NOT A VALID FIELD CODE
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'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
L48 19 L1 AND MICROGLIA#/AB,BI

=> dup rem l48

PROCESSING COMPLETED FOR L48
L49 7 DUP REM L48 (12 DUPLICATES REMOVED)

=> d 1- bib ab

YOU HAVE REQUESTED DATA FROM 7 ANSWERS - CONTINUE? Y/(N):y

L49 ANSWER 1 OF 7 MEDLINE DUPLICATE 1
AN 1999047653 MEDLINE
DN 99047653
TI Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation.
AU Qiu W Q; Walsh D M; Ye Z; Vekrellis K; Zhang J; Podlisny M B; Rosner M R; Safavi A; Hersh L B; Selkoe D J
CS Department of Neurology and Program in Neuroscience, Harvard Medical School and Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, Massachusetts 02115-5716, USA.
NC AG12749 (NIA)
DA 02243 (NIDA)
DA 07062 (NIDA)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Dec 4) 273 (49) 32730-8.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199903
EW 19990303
AB Excessive cerebral accumulation of the 42-residue amyloid beta-protein (Abeta) is an early and invariant step in the pathogenesis of Alzheimer's disease. Many studies have examined the cellular production of Abeta from its membrane-bound precursor, including the role of the ***presenilin*** proteins therein, but almost nothing is known about how Abeta is degraded and cleared following its secretion. We previously screened neuronal and nonneuronal cell lines for the production of proteases capable of degrading naturally secreted Abeta under biologically relevant conditions

and concentrations. The major such protease identified was a metalloprotease released particularly by a ***microglial*** cell line, BV-2. We have now purified and characterized the protease and find that it is indistinguishable from insulin-degrading enzyme (IDE), a thiol metalloendopeptidase that degrades small peptides such as insulin, glucagon, and atrial natriuretic peptide. Degradation of both endogenous and synthetic Abeta at picomolar to nanomolar concentrations was completely inhibited by the competitive IDE substrate, insulin, and by two other IDE inhibitors. Immunodepletion of conditioned medium with an IDE antibody removed its Abeta-degrading activity. IDE was present in BV-2 cytosol, as expected, but was also released into the medium by intact, healthy cells. To confirm the extracellular occurrence of IDE in vivo, we identified intact IDE in human cerebrospinal fluid of both normal and Alzheimer subjects. In addition to its ability to degrade Abeta, IDE activity was unexpectedly found be associated with a time-dependent oligomerization of synthetic Abeta at physiological levels in the conditioned media of cultured cells; this process, which may be initiated by IDE-generated proteolytic fragments of Abeta, was prevented by three different IDE inhibitors. We conclude that a principal protease capable of down-regulating the levels of secreted Abeta extracellularly is IDE.

L49 ANSWER 2 OF 7 MEDLINE DUPLICATE 2
AN 1998441028 MEDLINE
DN 98441028
TI [Alzheimer disease. Epidemiology, genetics and physiopathological hypotheses].
Maladie d'Alzheimer. Epidemiologie, genetique et hypoth`eses physiopathologiques.
AU Blain H; Jeandel C
CS Service de Medecine B, CHU Nancy-Brabois, Vandoeuvre.
SO PRESSE MEDICALE, (1998 Apr 18) 27 (15) 725-30. Ref: 99
Journal code: PMT. ISSN: 0755-4982.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA French
FS Priority Journals; Cancer Journals
EM 199901
EW 19990104
AB RISK FACTORS: Aging is the chief risk factor for Alzheimer's disease (AD).
Other risk factors are aluminum in drinking water, diabetes mellitus, head trauma. Protective factors are: higher education, cigarette smoking, nonsteroidal anti-inflammatory drugs and estrogen use. GENETIC FACTORS:
Mutations of ***presenilins*** 1 and 2 and of the APP gene in families with early-onset AD. Apolipoprotein E polymorphism in late-onset familial and sporadic AD. PATHOGENIC HYPOTHESES: Amyloid deposits in senile plaques and therefore dementia could be due to an overproduction of Abeta (Down's syndrome) or due to the primary (APP mutation) or secondary (role of diabetes, mellitus, apoE polymorphism: protective effect of estrogen) abnormal neurotoxic feature of Abeta. The hyperphosphorylation of tau (a protein which plays a pivotal role in the axonal transport), perhaps regulated by the apoE polymorphism could lead to neurofibrillar degeneration. Neurotoxic mediators produced by the activated ***microglia*** (perhaps activated by neuronal damage) and oxidative stress could also be involved in the neurodegeneration.

L49 ANSWER 3 OF 7 MEDLINE
AN 1998210340 MEDLINE
DN 98210340
TI Molecular physiopathology of Alzheimer's disease.
AU Yamada T
CS Department of Neurology, Faculty of Medicine, Kyushu University, Fukuoka.
SO FUKUOKA IGAKU ZASSHI. FUKUOKA ACTA MEDICA, (1998 Feb) 89 (2) 29-33. Ref:
5
Journal code: F8R. ISSN: 0016-254X.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Japanese
EM 199808
EW 19980803

L49 ANSWER 4 OF 7 MEDLINE DUPLICATE 3
AN 1998330346 MEDLINE
DN 98330346
TI Lack of specific association of ***presenilin*** 1 (PS-1) protein with plaques and tangles in Alzheimer's disease.
AU Xia M Q; Berezovska O; Kim T W; Xia W M; Liao A; Tanzi R E; Selkoe D;
Hyman B T
CS Alzheimer's Research Unit, Department of Neurology, Massachusetts General Hospital-East, Charlestown 02129, USA.
NC AG05134 (NIA)
AG08487 (NIA)
AG14744 (NIA)
SO JOURNAL OF THE NEUROLOGICAL SCIENCES, (1998 Jun 11) 158 (1) 15-23.
Journal code: JBJ. ISSN: 0022-510X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
EW 19981203
AB Missense mutations in the ***presenilin*** -1 (PS-1) gene are causally related to the majority of familial early-onset Alzheimer's disease (FAD).
PS-1 immunohistochemical expression in normal human brain and in brains with Alzheimer's disease (AD) has so far been controversial. Here, we report a study of PS-1 expression in brains, cell lines and peripheral blood mononuclear cells using a panel of well characterized PS-1-specific antibodies. These antibodies were characterized by immunofluorescent staining of PS-1 transfectants followed by flow cytometric analysis. In human brain, widespread neuronal staining was observed. PS-1 immunoreactivity was primarily confined to neuronal cell bodies and proximal dendrites. Weaker staining of ***microglia*** was also detected, in accord with the finding of PS-1 immunoreactivity in monocytes. PS-1 expression is not particularly associated with neurons either containing or spared from neurofibrillary tangles, nor with senile plaques. The level of PS-1 expression does not differ between normal and AD brains. Immunoprecipitation from AD, FAD and control brains revealed only a 32 kDa N-terminal fragment and an 18-20 kDa C-terminal fragment. Little or no full length PS-1 was detected. The enriched presence of PS-1 in neurons implies an important role in neuronal function, however, the lack of apparent association of its expression with AD pathology signifies the need for a better understanding of its pathophysiological role.

L49 ANSWER 5 OF 7 MEDLINE DUPLICATE 4
AN 1998348622 MEDLINE
DN 98348622
TI Amyotrophic lateral sclerosis and Alzheimer disease. Lessons from model systems.
AU Price D L; Wong P C; Borchelt D R; Pardo C A; Thinakaran G;

Doan A P; Lee
M K; Martin L J; Sisodia S S
CS Department of Pathology, Johns Hopkins, University School of Medicine,
Baltimore, Maryland 21205-2196, USA.
NC NS 20471 (NINDS)
AG 05146 (NIA)
NS 10580 (NINDS)
+
SO REVUE NEUROLOGIQUE, (1997 Sep) 153 (8-9) 484-95. Ref: 145
Journal code: SU9. ISSN: 0035-3787.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199810
EW 19981003
AB The human neurodegenerative diseases, including motor neuron disease and
Alzheimer's disease (AD), are characterized by a selective involvement of
certain regions of the brain/spinal cord and selected populations of
neurons. Sporadic amyotrophic lateral sclerosis (ALS) is an age-associated
disease with cytoskeletal abnormalities and death of motor neurons;
familial ALS (FALS), an autosomal dominant disease linked to mutations in
superoxide dismutase 1 (SOD1), is manifested by inclusions and
degeneration of motor neurons. Autosomal dominant familial AD (FAD),
linked to mutations in ***presenilin*** (PS1 and PS2) genes or the
amyloid precursor protein (APP) gene, shows brain abnormalities (e.g.,
neurofibrillary tangles, deposits of .-amyloid A., and death of subsets of
neurons) similar to those that occur in sporadic AD, the risk of which is
enhanced by the presence of one or two copies of apolipoprotein E4 (apoE4)
alleles. To examine the mechanisms of these diseases, investigators have
used a variety of animal models, including experimentally produced,
spontaneously occurring, or genetically engineered models of disease.
Studies of models of degeneration of motor neurons (axotomy) and
cytoskeletal abnormalities seen in motor neuron disease (i.e., axonopathy
induced by .,.'-iminodipropionitrile (IDPN), hereditary canine spinal
muscular atrophy (HCSMA), and neurofilament NF transgenic Tg mice) have
demonstrated that NF-filled swellings of axons are related to alterations
in the biology of NF transport. Tg mice with SOD1 mutations, which develop
the clinical features of FALS, show selective degeneration of motor
neurons, which is attributed to the acquisition of toxic properties by
mutant SOD1. Models of AD include: aged monkeys that show both
cognitive/memory deficits and cellular abnormalities (amyloid
deposition/cytoskeletal abnormalities of neurons) in cortex and
hippocampus; and Tg mice that express mutant human FAD-linked genes (i.e.,
APP and PS1) and show increased levels of A.42, amyloid deposits,
dystrophic neurites, and local responses of astrocytes and
microglia . This review discusses the behavioral/neuropathological
features of AD, the results of investigations of mechanisms of disease in
model systems, and potential utility of some of these models for testing
new therapies.

L49 ANSWER 6 OF 7 MEDLINE DUPLICATE 5
AN 97343985 MEDLINE
DN 97343985
TI Immunoreactivity of ***presenilin*** -1 in human, rat and mouse brain.
AU Kim K S; Wegiel J; Sapienza V; Chen J; Hong H; Wisniewski H M
CS New York State Institute for Basic Research in Developmental Disabilities,
Staten Island 10314, USA.
NC PO1-AG11531 (NIA)
SO BRAIN RESEARCH, (1997 May 16) 757 (1) 159-63.
Journal code: B5L. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
AB Monoclonal antibodies (mAbs) D3G6 and C8A5, specific for amino acid
residues 160-168 of S182 protein, immunolabeled neurons, ependymal and
choroid plexus cells, and myocytes in brain sections from normal subjects
and people with Alzheimer disease or Down syndrome and in rats and mice.
Oligodendroglia, ***microglia*** , and the majority of astrocytes were
negative. S182 protein or a fragment of the protein detected with these
mAbs is not a constituent of amyloid-beta deposits or tangles.

L49 ANSWER 7 OF 7 CAPLUS COPYRIGHT 1999 ACS
AN 1998:109324 CAPLUS
DN 128:163691
TI Central role of oxyradicals in the mechanism of amyloid b-peptide cytotoxicity
AU Mattson, Mark P.
CS Sanders-Brown Res. Cent. on Aging and Dep. Anatomy & Neurobiol., Univ.
Kentucky, Lexington, KY, 40636-0230, USA
SO Alzheimer's Dis. Rev. (1997), 2(1/2), 1-14
CODEN: ADREFN
URL: http://www.coa.uky.edu/ADReview/Mattson.htm
PB Sanders-Brown Center on Aging, University of Kentucky
DT Journal; General Review; (online computer file)
LA English
AB A review and discussion with many refs. Overwhelming evidence indicates
that cells in Alzheimer's disease brain are subjected to abnormally high
levels of oxidative stress, and that amyloids are a focus of cellular and
mol. oxidn. Recent studies suggest that amyloid b-peptide (Ab) plays a
major role in promoting oxidative stress in neurons and glial cells, and
that such oxidative stress can account for many of the metabolic and
neurodegenerative alterations obsd. in AD brain. Ab induces membrane
lipid peroxidn. in neurons which leads to impairment of ion-motive
ATPases, and glutamate and glucose transporters. These actions of Ab lead
to membrane depolarization and energy failure which, in turn, promote
excitotoxic and apoptotic degenerative depolarization and energy failure
which, in turn, promote excitotoxic and apoptotic degenerative cascades
involving calcium overload. Membrane oxidn., as induced by Ab, also
disrupts coupling of metabotropic receptors to their GTP-binding proteins,
which may account for the well-known cholinergic signaling deficits and
assocd. cognitive impairment in AD. 4-Hydroxynonenal, an aldehydic prodn.
of membrane lipid peroxidn., is implicated as a mediator of Ab-induced
disruption of cellular ion and energy homeostasis, and neuronal apoptosis.
Oxidative stress induced by Ab in ***microglia*** and astrocytes
likely contributes to the inflammatory process in AD brain. Moreover,
Ab-mediated oxidative damage to vascular endothelial cells may contribute
to the impaired glucose transport and compromised barrier function of the
cerebral vessels in AD. Finally, the possible mechanistic links between
mutations in ***presenilin*** genes, oxidative stress, and

neuronal
degeneration in AD are considered.

=> s l1 and glia#/ab,bi

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L50 41 L1 AND GLIA#/AB,BI

=> dup rem l50

PROCESSING COMPLETED FOR L50
L51 23 DUP REM L50 (18 DUPLICATES REMOVED)

=> s l50 and presenilin-2/ab,bi

'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
L52 16 L50 AND PRESENILIN-2/AB,BI

=> dup rem l52

PROCESSING COMPLETED FOR L52
L53 7 DUP REM L52 (9 DUPLICATES REMOVED)

=> d 1- bib ab

YOU HAVE REQUESTED DATA FROM 7 ANSWERS - CONTINUE? Y/(N):y

L53 ANSWER 1 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1999:52671 BIOSIS
DN PREV199900052671
TI Double transgenic mice carrying mutant amyloid beta precursor protein and
presenilin 1 genes express accelerated Alzheimer-like phenotype.
AU Sugaya, K. (1); Jerome, S. (1); Bryan, D.; McKinney, M.; Duff, K.; Kumar,
V. (1)
CS (1) Westside VA Med. Cent., Chicago, IL 60612 USA
SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 728.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1
Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience
. ISSN: 0190-5295.
DT Conference
LA English

L53 ANSWER 2 OF 7 MEDLINE DUPLICATE 1
AN 1998194679 MEDLINE
DN 98194679
TI Profiles of amyloid precursor and ***presenilin*** ***2*** -like
proteins are correlated during development of the mouse hypothalamus.
AU Apert C; Czech C; Faivre-Bauman A; Loudes C; Pradier L; Epelbaum J
CS Inserm U159, Centre Paul Broca, Paris, France.
SO JOURNAL OF NEUROENDOCRINOLOGY, (1998 Feb) 10 (2) 101-9.
Journal code: BRL. ISSN: 0953-8194.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199807
EW 19980703
AB The amyloid precursor protein (APP) and APP-like (APLP) material, as
visualized with the Mab22C11 antibody, have previously been shown to be
associated with radial ***glia*** in hypothalamus, which are known to
promote neurite outgrowth. By Northern blot analysis, APP 695 mRNA levels
increased steadily over hypothalamic development, APP 770 mRNA was
transiently expressed at 12 days postnatally, and APLP mRNA was only
weakly expressed in the hypothalamus. The developmental pattern of APP
moeities in mouse hypothalamus and in fetal hypothalamic neurons in
culture was compared with a ***presenilin*** ***2*** (PS2) related
protein using an antibody developed against the N-terminal part of PS2. By
Western blot analysis, APP and PS2-like immunoreactivity were visualized
as a 100-130 and 52 kDa bands, respectively. An APP biphasic increase was
observed during hypothalamic development in vivo. APP immunoreactivity was
equally detected in neuronal and ***glial*** cultures, while PS2-like
material was more concentrated in neurons. A correlation between
APP/APP-like and PS2-like levels was observed during development in vivo.
While APP was mostly associated with membrane fractions, a significant
portion of PS2-like material was also recovered from cytosolic fractions
in vitro. In contrast to native PS2 in COS-transfected cells, the PS2-like
material did not aggregate after heating for 90 s at 90 degrees C. These
results indicate a close association between APP and PS2-like material
during hypothalamic development in vivo, and suggest that neuronal and
glial cultures may provide appropriate models to test their
interactions.

L53 ANSWER 3 OF 7 MEDLINE
AN 1998087486 MEDLINE
DN 98087486
TI Accelerated Alzheimer-type phenotype in transgenic mice carrying both
mutant amyloid precursor protein and ***presenilin*** 1 transgenes.
AU Holcomb L; Gordon M N; McGowan E; Yu X; Benkovic S; Jantzen P; Wright K;
Saad I; Mueller R; Morgan D; Sanders S; Zehr C; O'Campo K; Hardy J; Prada
C M; Eckman C; Younkin S; Hsiao K; Duff K
CS Department of Pharmacology, University of South Florida, Tampa 33612, USA.
NC AG146133 (NIA)
NS 33249 (NINDS)
SO NATURE MEDICINE, (1998 Jan) 4 (1) 97-100.
Journal code: CG5. ISSN: 1078-8956.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199803
EW 19980305
AB Genetic causes of Alzheimer's disease (AD) include mutations in the
amyloid precursor protein (APP), ***presenilin*** 1 (PS1), and
presenilin ***2*** (PS2) genes. The mutant APP(K670N,M671L)
transgenic line, Tg2576, shows markedly elevated amyloid beta-protein (A
beta) levels at an early age and, by 9-12 months, develops extracellular
AD-type A beta deposits in the cortex and hippocampus. Mutant PS1
transgenic mice do not show abnormal pathology, but do display subtly
elevated levels of the highly amyloidogenic 42- or 43-amino acid peptide A
beta42(43). Here we demonstrate that the doubly transgenic progeny from a
cross between line Tg2576 and a mutant PS1M146L transgenic line develop
large numbers of fibrillar A beta deposits in cerebral cortex and
hippocampus far earlier than their singly transgenic Tg2576 littermates.
In the period preceding overt A beta deposition, the doubly transgenic
mice show a selective 41% increase in A beta42(43) in their brains.

Thus,
the development of AD-like pathology is substantially enhanced when a PS1
mutation, which causes a modest increase in A beta42(43), is introduced
into Tg2576-derived mice. Remarkably, both doubly and singly transgenic
mice showed reduced spontaneous alternation performance in a "Y" maze
before substantial A beta deposition was apparent. This suggests that some
aspects of the behavioral phenotype in these mice may be related to an
event that precedes plaque formation.

L53 ANSWER 4 OF 7 CAPLUS COPYRIGHT 1999 ACS
AN 1998:1559 CAPLUS
DN 128:73898
TI Transgenic animals expressing perlecan and amyloid genes at high levels
and methods of identifying compounds for the treatment of amyloidoses
IN Snow, Alan; Fukuchi, Ken-ichiro; Hassell, John
PA University of Washington, USA
SO PCT Int. Appl., 146 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9746664	A1	19971211	WO 97-US9875	19970606
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9736402	A1	19980105	AU 97-36402	19970606
PRAI US 96-17830		19960606		
WO 97-US9875		19970606		

AB Transgenic animals expressing a foreign gene for a perlecan, or genes for
perlecan and an amyloid are constructed for use in the testing of compds.
that can alter the rate or extent of amyloid deposition. Over-expression
of perlecan and amyloid proteins results in animals showing symptoms
closer to amyloidoses than found in animals only over-expressing an
amyloid gene, esp. Alzheimer's disease. Over-expression of a gene
encoding domains I-V of mouse perlecan and the 695-amino acid isoform of
.beta.-amyloid in P19 cells led to an up-regulation of .beta.-amyloid
synthesis and secretion. P19 cells induced to form neurons degenerated
when the perlecan gene was overexpressed.

L53 ANSWER 5 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:468096 BIOSIS
DN PREV199799767299
TI Expression of Alzheimer's disease related genes in three human astrocytic
cell lines.
AU Shepherd, C. E.; Calvert, E. L.; Cambray-Deakin, M. A.; Pearson, R. C. A.
CS Dep. Biomedical Sci., Univ. Sheffield, S10 2TN UK
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 266.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1
New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

L53 ANSWER 6 OF 7 MEDLINE DUPLICATE 2
AN 97347186 MEDLINE
DN 97347186
TI Immunohistochemical analysis of ***presenilin*** ***2*** expression in the mouse brain: distribution pattern and co-localization
with ***presenilin*** 1 protein.
AU Blanchard V; Czech C; Bonici B; Clavel N; Gohin M; Dalet K; Revah F;
Pradier L; Imperato A; Moussaoui S
CS Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Vitry-sur-Seine, France.
SO BRAIN RESEARCH, (1997 May 30) 758 (1-2) 209-17.
Journal code: B5L. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
EW 19971103
AB Missense mutations of ***presenilin*** 1 (PS-1) and ***presenilin***
2 (PS-2) genes cause the majority of early-onset familial forms of
Alzheimer's disease (AD). We previously characterized the distribution of
the PS-1 protein in the mouse brain by immunohistochemistry using an
antibody directed against an epitope located in the large hydrophilic loop
[Moussaoui, S., Czech, C., Pradier, L., Blanchard, V., Bonici, B., Gohin,
M., Imperato, A. and Revah, F., Immunohistochemical analysis of
presenilin 1 expression in the mouse brain, FEBS Lett., 383 (1996)
219-222]. Similarly, we now report the distribution pattern of PS-2
protein in the mouse brain. For these experiments we used a polyclonal
antibody raised against a synthetic peptide corresponding to the
amino-acid sequence 7-24 of the predicted human PS-2 protein. The
specificity of the antibody was evidenced by its ability to recognize PS-2
protein in immunoprecipitation studies and by antigen-peptide competition.
In the mouse brain, PS-2 protein was present in numerous cerebral
structures, but its distribution in these structures did not correlate
with their susceptibility to AD pathology. In all examined structures of
the gray matter, PS-2 protein was concentrated in neuronal cell bodies but
it was not detected in the ***glial*** cells of the white matter. The
regional distribution pattern of PS-2 protein was almost identical to that
of PS-1 protein. Moreover, PS-2 protein co-localized with PS-1 protein in
a large number of neuronal cell bodies. In terms of subcellular
localization, PS-2 immunostaining was present almost exclusively in
neuronal cell bodies while PS-1 immunostaining was also present in
dendrites. This could be explained by the different epitopes of the
antibodies and the known proteolytic processing of both
presenilins in vivo [Tanzi, R.E., Kovacs, D.M., Kim, T.-W., Moir,
R.D., Guenette, S.Y. and Wasco, W., The ***presenilin*** genes and
their role in early-onset familial Alzheimer's disease, Alzheimer's
disease Rev., 1 (1996) 91-98]. Within neuronal cell bodies, the
immunostaining of PS-2 protein, as well as that of PS-1 protein, had a
reticular and granular appearance. This suggests in agreement with
previous observations on PS-1 and PS-2 in COS and H4 cells [Kovacs, D.M.,
Fausett, H.J., Page, K.J., Kim, T.-W., Moir, R.D., Merriam, D.E.,
Hollister, R.D., Hallmark, O.G., Mancini, R., Felsenstein, K.M., Hyman,
B.T., Tanzi, R.E., Wasco, W., Alzheimer-associated ***presenilins*** 1
and 2: neuronal expression in brain and localization to intracellular
membranes in mammalian cells, Nature Med., 2 (1996) 224-229] that these
proteins are situated in intracytoplasmic organelles, possibly the

endoplasmic reticulum and the Golgi complex.

L53 ANSWER 7 OF 7 MEDLINE DUPLICATE 3
AN 97081125 MEDLINE
DN 97081125
TI Expression of ***presenilin*** 1 and 2 (PS1 and PS2) in human and
murine tissues.
AU Lee M K; Slunt H H; Martin L J; Thinakaran G; Kim G; Gandy S E; Seeger M;
Koo E; Price D L; Sisodia S S
CS Department of Pathology, The Johns Hopkins University School of Medicine,
Baltimore, Maryland 21205, USA.
NC AG05146 (NIA)
NS20471 (NINDS)
SO JOURNAL OF NEUROSCIENCE, (1996 Dec 1) 16 (23) 7513-25.
Journal code: JDF. ISSN: 0270-6474.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199703
EW 19970302
AB Mutations in genes encoding related proteins, termed ***presenilin***
1 (PS1) and ***presenilin*** ***2*** (PS2), are linked to the
majority of cases with early-onset familial Alzheimer's disease (FAD). To
clarify potential function(s) of ***presenilins*** and relationships
of ***presenilin*** expression to pathogenesis of AD, we examined the
expression of PS1 and PS2 mRNA and PS1 protein in human and mouse.
Semi-quantitative PCR of reverse-transcribed RNA (RT-PCR) analysis
revealed that PS1 and PS2 mRNA are expressed ubiquitously and at
comparable levels in most human and mouse tissues, including adult brain.
However, PS1 mRNA is expressed at significantly higher levels in
developing brain. In situ hybridization studies of mouse embryos revealed
widespread expression of PS1 mRNA with a neural expression pattern that,
in part, overlaps that reported for mRNA encoding specific Notch homologs.
In situ hybridization analysis in adult mouse brain revealed that PS1 and
PS2 mRNAs are enriched in neurons of the hippocampal formation and
entorhinal cortex. Although PS1 and PS2 mRNA are expressed most
prominently in neurons, lower but significant levels of PS1 and PS2
transcripts are also detected in white matter ***glial*** cells.
Moreover, cultured neurons and astrocytes express PS1 and PS2 mRNAs. Using
PS1-specific antibodies in immunoblot analysis, we demonstrate that PS1
accumulates as approximately 28 kDa N-terminal and approximately 18 kDa
C-terminal fragments in brain. Immunocytochemical studies of mouse brain
reveal that PS1 protein accumulates in a variety of neuronal populations
with enrichment in somatodendritic and neuropil compartments.

=> s l1 and neuron?/ab,bi

'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
L54 500 L1 AND NEURON?/AB,BI

=> s l54 and presenilin-2/ab,bi

'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
L55 135 L54 AND PRESENILIN-2/AB,BI

=> s l55 and (cell death or apoptosis)/ab,bi

'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
'AB' IS NOT A VALID FIELD CODE
L56 43 L55 AND (CELL DEATH OR APOPTOSIS)/AB,BI

=> dup rem l56

PROCESSING COMPLETED FOR L56
L57 23 DUP REM L56 (20 DUPLICATES REMOVED)

=> d l- bib ab

YOU HAVE REQUESTED DATA FROM 23 ANSWERS - CONTINUE? Y/(N):y

L57 ANSWER 1 OF 23 MEDLINE DUPLICATE 1
AN 1999145560 MEDLINE
DN 99145560
TI Phosphorylation of ***presenilin*** - ***2*** regulates its cleavage
by caspases and retards progression of ***apoptosis*** .
AU Walter J; Schindzielorz A; Grunberg J; Haass C
CS Central Institute of Mental Health, Department of Molecular Biology, J5,
68159 Mannheim, Germany.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF
AMERICA, (1999 Feb 16) 96 (4) 1391-6.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199905
EW 19990504
AB Mutations within the ***Presenilin*** - ***2*** (PS-2) gene are
associated with early onset familial Alzheimer's disease. The gene encodes
a polytopic transmembrane protein that undergoes endoproteolytic
processing resulting in the generation of N-terminal and C-terminal
fragments (CTFs). PS-2 is also cleaved by proteases of the caspase family
during apoptotic ***cell*** ***death*** . CTFs of PS-2 were shown
to inhibit ***apoptosis*** , suggesting an important role in the
regulation of programmed ***cell*** ***death*** . Recently, we
found that the CTF of PS-2 is phosphorylated in vivo. We mapped the in
vivo phosphorylation sites of PS-2 to serine residues 327 and 330, which
are localized immediately adjacent to the cleavage sites of caspases after
aspartate residues 326 and 329. Phosphorylation of PS-2 inhibits its
cleavage by caspase-3. This effect can be mimicked by substitutions of
serines 327 and 330 by aspartate or glutamate. In addition, the
uncleavable form of PS-2 CTF was found to enhance its antiapoptotic
properties, leading to a slower progression of ***apoptosis*** . These
results demonstrate that PS-2 cleavage as well as its function in
apoptosis can be regulated by protein phosphorylation. Alterations
in the phosphorylation of PS-2 may therefore promote the pathogenesis of
AD by affecting the susceptibility of ***neurons*** to apoptotic
stimuli.

L57 ANSWER 2 OF 23 MEDLINE DUPLICATE 2
AN 1999098950 MEDLINE
DN 99098950
TI Contrasting role of ***presenilin*** -1 and ***presenilin*** -
2 in ***neuronal*** differentiation in vitro.
AU Hong C S; Caromile L; Nomata Y; Mori H; Bredesen D E; Koo E H
CS Department of Neurosciences, University of California, San

Diego, La
Jolla, California 92093, USA.
NC NS01812 (NINDS)
AG12282 (NIA)
SO JOURNAL OF NEUROSCIENCE, (1999 Jan 15) 19 (2) 637-43.

Journal code: JDF. ISSN: 0270-6474.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
EW 19990403
AB ***Presenilin*** -1 (PS1) and ***presenilin*** - ***2*** (PS2),
the major genes of familial Alzheimer's disease, are homologous to sel-12,
a Caenorhabditis elegans gene involved in cell fate decision during development. Recently, wild-type and mutant ***presenilins*** have
been associated also with apoptotic ***cell*** ***death*** . By
using stable transfection of antisense cDNAs, we studied the functions of
PS1 and PS2 during ***neuronal*** differentiation in the NTera2 human
teratocarcinoma (NT2) cell line. Expression of antisense PS1 resulted in a
failure of the clones to differentiate into ***neurons*** after
retinoic acid induction, whereas cells transfected with antisense PS2
differentiated normally. Concomitantly, antisense PS1 clones were
associated with increased ***apoptosis*** both under basal conditions
and during the early period of ***neuronal*** differentiation after
retinoic acid treatment. Overexpression of bcl-2 in antisense PS1 clones
reduced ***cell*** ***death*** and resulted in a recovery of
neuronal differentiation. These studies suggest that PS1 plays a
role in differentiation and ***cell*** ***death*** and that PS1
and PS2 have differing physiological roles in this experimental paradigm.

L57 ANSWER 3 OF 23 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.DUPLICATE 3
AN 1999088629 EMBASE
TI The ***presenilins*** .
AU Mattson M.P.; Guo Q.
CS Dr. M.P. Mattson, 211 Sanders-Brown Building, University of Kentucky,
Lexington, KY 40536-0230, United States.
mmattson@aging.coa.uky.edu
SO Neuroscientist, (1999) 5/2 (112-124).
Refs: 61
ISSN: 1073-8584 CODEN: NROSFJ
CY United States
DT Journal; General Review
FS 008 Neurology and Neurosurgery
LA English
SL English
AB ***Presenilin*** -1 and ***presenilin*** - ***2*** are highly
homologous genes located on chromosomes 14 and 1, respectively, that have
recently been linked to some cases of early-onset autosomal dominant
inherited forms of Alzheimer's disease (AD). ***Presenilins*** are
integral membrane proteins localized in the endoplasmic reticulum of
neurons throughout the nervous system. Studies of
presenilin -1 knockout mice, and of invertebrate homologues of
presenilins and their interacting proteins, suggest major roles
for ***presenilins*** in normal development.
Presenilin -1
mutant knockin mice do not exhibit developmental abnormalities, which
indicates that the pathogenic mechanism of ***presenilin*** mutations
involves gain of an adverse property of the mutant protein. Expression of
presenilin mutations in cultured ***neurons*** and transgenic
mice results in increased sensitivity to ***apoptosis*** induced by
trophic factor withdrawal and exposure to oxidative and metabolic insults,
and also alters gene expression. The pathogenic mechanism of
presenilin mutations may involve perturbed endoplasmic reticulum
calcium homeostasis resulting in enhanced oxidative stress, altered
proteolytic processing of the amyloid precursor protein (APP), and
increased ***neuronal*** vulnerability to excitotoxicity. Studies of
presenilins are rapidly increasing our understanding the molecular
and cellular underpinnings of AD and are also elucidating novel roles of
the endoplasmic reticulum in ***neuronal*** plasticity and
cell ***death*** .

L57 ANSWER 4 OF 23 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1999049702 EMBASE
TI Alzheimer's disease and stroke.
AU Dineley K.; Denner L.
CS L. Denner, Texas Biotechnology Corporation, 7000 Fannin, Houston, TX
77030, United States. ldenner@tbc.com
SO IDrugs, (1999) 2/1 (7-8).
ISSN: 1369-7056 CODEN: IDRUFN
CY United Kingdom
DT Journal; Conference Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
037 Drug Literature Index
LA English
SL English
AB This report focuses on the two most common neurological diseases in man:
Alzheimer's disease (AD) and stroke. One common feature of both of these
diseases is the death of cells, particularly ***neurons*** . Since a
typical mechanism of ***cell*** ***death*** is ***apoptosis***
, this will be an additional focal point in this report.

L57 ANSWER 5 OF 23 MEDLINE
AN 1998401687 MEDLINE
DN 98401687
TI Is ***apoptosis*** key in Alzheimer's disease? [news] [see comments].
CM Comment in: Science 1998 Nov 13;282(5392):1268-9
AU Barinaga M
SO SCIENCE, (1998 Aug 28) 281 (5381) 1303-4.
Journal code: UJ7. ISSN: 0036-8075.
CY United States
DT News Announcement
LA English
FS Cancer Journals; Priority Journals
EM 199811

L57 ANSWER 6 OF 23 MEDLINE DUPLICATE 4
AN 1998442695 MEDLINE
DN 98442695
TI Calsenilin: a calcium-binding protein that interacts with the ***presenilins*** and regulates the levels of a ***presenilin***
fragment [see comments].
CM Comment in: Nat Med 1998 Oct;4(10):1127-8
AU Buxbaum J D; Choi E K; Luo Y; Lilliehook C; Crowley A C; Merriam D E;
Wasco W
CS Department of Psychiatry, Mount Sinai School of Medicine, New York, New
York 10029, USA.. buxbaj01@doc.mssm.edu
SO NATURE MEDICINE, (1998 Oct) 4 (10) 1177-81.
Journal code: CG5. ISSN: 1078-8956.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199901

EW 19990104
AB Most early-onset familial Alzheimer disease (AD) cases are caused by
mutations in the highly related genes ***presenilin*** 1 (PS1) and
presenilin ***2*** (PS2). ***Presenilin*** mutations
produce increases in beta-amyloid (Abeta) formation and ***apoptosis***
in many experimental systems. A cDNA (ALG-3) encoding the last 103 amino
acids of PS2 has been identified as a potent inhibitor of
apoptosis . Using this PS2 domain in the yeast two-hybrid system,
we have identified a ***neuronal*** protein that binds calcium and
presenilin , which we call calsenilin. Calsenilin interacts with
both PS1 and PS2 in cultured cells, and can regulate the levels of a
proteolytic product of PS2. Thus, calsenilin may mediate the effects of
wild-type and mutant ***presenilins*** on ***apoptosis*** and on
Abeta formation. Further characterization of calsenilin may lead to an
understanding of the normal role of the ***presenilins*** and of the
role of the ***presenilins*** in Alzheimer disease.

L57 ANSWER 7 OF 23 MEDLINE DUPLICATE 5
AN 1999025290 MEDLINE
DN 99025290
TI Familial Alzheimer's disease: oxidative stress, beta-amyloid,
presenilins , and ***cell*** ***death*** .
AU Velez-Pardo C; Jimenez Del Rio M; Lopera F
CS Department of Neurology, University Hospital, Medellin, Colombia.
SO GENERAL PHARMACOLOGY, (1998 Nov) 31 (5) 675-81. Ref: 108
Journal code: FLK. ISSN: 0306-3623.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199902
EW 19990204
AB 1. The basic etiology of Alzheimer's disease remains unknown, although
four genes have so far been involved: beta-amyloid precursor protein,
presenilin -1, ***presenilin*** - ***2*** and apolipoprotein
E genes. 2. The largest familial Alzheimer's disease (FAD) kindred so far
reported belong to a point mutation in codon 280 that results in a
glutamic acid-to-alanine substitution in ***presenilin*** -1
characterized in Antioquia, Colombia. 3. A hypothetical unified molecular
mechanism model of ***cell*** ***death*** in FAD mediated by
presenilin -1, beta-amyloid, and oxidative stress is proposed as an
attempt to explain the mechanisms of ***neuronal*** loss in this
neurodegenerative disorder.

L57 ANSWER 8 OF 23 MEDLINE
AN 1998439039 MEDLINE
DN 98439039
TI ***Presenilins*** --in search of functionality.
AU Karran E H; Allsop D; Christie G; Davis J; Gray C; Mansfield F; Ward R V
CS Neurosciences Research, SmithKline Beecham Pharmaceuticals, New Frontiers
Science Park, Harlow, Essex, UK.
SO BIOCHEMICAL SOCIETY TRANSACTIONS, (1998 Aug) 26 (3) 491-6. Ref: 48
Journal code: E48. ISSN: 0300-5127.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199902
EW 19990204
AB The discovery of the PS proteins, the complexities of their biochemistry
and their potential involvement in signalling pathways and in
apoptosis have galvanized research into AD. To date, the aspect of
the functionality of the PSs most relevant to the pathology of AD is the
effect of PS FAD mutants to increase the proportion of A beta 42 produced
from cells. This, coupled to the observation that gamma-secretase cleavage
is considerably reduced in ***neurons*** derived from PS-1 knockout
mice, argues strongly that PS plays a very direct role in the proteolytic
processing of APP.

L57 ANSWER 9 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1998:224560 BIOSIS
DN PREV199800224560
TI Regulation of ***apoptosis*** by ***presenilin*** 1.
AU Wolozin, Benjamin (1); Alexander, P.; Palacino, J.
CS (1) Dep. Pharmacol., Loyola Univ. Medical Cent., Build. 102, Room 3634,
2160 South First Ave., Maywood, IL 60153 USA
SO Neurobiology of Aging, (Jan.-Feb., 1998) Vol. 19, No. 1 SUPPL., pp.
S23-S27.
ISSN: 0197-4580.
DT Article
LA English
AB Familial Alzheimer's disease is transmitted as an autosomal dominant
disorder and, in 5-10% of the cases, is caused by mutations in the coding
regions of two homologous genes, ***Presenilin*** 1 and 2 (PS1 and
PS2). Previously, we have shown that PS2, a homolog of PS1, regulates
apoptosis induced in ***neurons*** by trophic withdrawal or
Abeta, and in T-cells by Fas ligand. We now report that PS1 also regulates
apoptosis . Both wild-type and the H115Y mutant form of PS1 enhance
Fas-mediated ***apoptosis*** in Jurkat cells. We also observed that
wild-type and the H115Y mutant form of PS1 differentially regulate Jun
Kinase, an important enzyme regulating ***apoptosis*** .

L57 ANSWER 10 OF 23 MEDLINE DUPLICATE 6
AN 1998082804 MEDLINE
DN 98082804
TI ***Presenilins*** , the endoplasmic reticulum, and ***neuronal***
apoptosis in Alzheimer's disease.
AU Mattson M P; Guo Q; Furukawa K; Pedersen W A
CS Department of Anatomy and Neurobiology, University of Kentucky, Lexington
40536-0230, USA.
NC AG14554 (NIA)
AG05144 (NIA)
AG05119 (NIA)
+
SO JOURNAL OF NEUROCHEMISTRY, (1998 Jan) 70 (1) 1-14. Ref: 105
Journal code: JAV. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199804
EW 19980401
AB Many cases of autosomal dominant inherited forms of early-onset
Alzheimer's disease are caused by mutations in the genes encoding
presenilin -1 (PS-1; chromosome 14) and ***presenilin*** -
2 (PS-2; chromosome 1). PSs are expressed in

neurons
throughout the brain wherein they appear to be localized primarily to the
endoplasmic reticulum (ER) of cell bodies and dendrites. PS-1 and PS-2
show high homology and are predicted to have eight transmembrane domains
with the C terminus, N terminus, and a loop domain all on the cytosolic
side of the membrane; an enzymatic cleavage of PSs occurs at a site near
the loop domain. The normal function of PSs is unknown, but data suggest
roles in membrane trafficking, amyloid precursor protein processing, and
regulation of ER calcium homeostasis. Homology of PSs to the C. elegans
gene sel-12, which is involved in Notch signaling, and phenotypic
similarities of PS-1 and Notch knockout mice suggest a developmental role
for PSs in the nervous system. When expressed in cultured cells and
transgenic mice, mutant PSs promote increased production of a long form of
amyloid beta-peptide (A beta1-42) that may possess enhanced amyloidogenic
and neurotoxic properties. PS mutations sensitize cultured neural cells to
apoptosis induced by trophic factor withdrawal, metabolic insults,
and amyloid beta-peptide. The mechanism responsible for the proapoptotic
action of mutant PSs may involve perturbed calcium release from ER stores
and increased levels of oxidative stress. Recent studies of
apoptosis in many different cell types suggest that ER calcium
signaling can modulate ***apoptosis*** . The evolving picture of PS
roles in ***neuronal*** plasticity and Alzheimer's disease is bringing
to the forefront the ER, an organelle increasingly recognized as a key
regulator of ***neuronal*** plasticity and survival.

L57 ANSWER 11 OF 23 MEDLINE DUPLICATE 7
AN 1998346881 MEDLINE
DN 98346881
TI Localization and possible functions of ***presenilins*** in brain.
AU McGeer P L; Kawamata T; McGeer E G
CS Kinsmen Laboratory of Neurological Research, University of British
Columbia, Vancouver, Canada.
SO REVIEWS IN THE NEUROSCIENCES, (1998) 9 (1) 1-15.
Ref: 83
Journal code: BYT. ISSN: 0334-1763.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199811
EW 19981104
AB ***Presenilin*** -1 (PS-1) is localized to chromosome 14 and
presenilin - ***2*** (PS-2) to chromosome 1. Mutations in these
genes, primarily in PS-1, account for an estimated 60% of early onset
familial Alzheimer's disease cases (FAD), while FAD cases account for
about 10% of all Alzheimer's disease (AD) cases. The mutations are minor
but are 100% penetrant, suggesting that the proteins have acquired a toxic
gain in function. The proteins have multiple transmembrane domains and
have been reported to be localized to the Golgi apparatus, endoplasmic
reticulum, nuclear membranes and cell surface membranes. They are thought
to have functions associated with vesicular trafficking, Notch signaling
and ***apoptosis*** . PS mutants show relative increases in the amount
of A beta42/43 compared with A beta40 in plasma, fibroblasts and brain,
observations which have been taken as a possible mechanism of their role
in AD. In brain, the mRNAs for these two genes are localized primarily in
neurons , with the strongest in situ hybridization signals being
observed in the hippocampus, cerebellum and cerebral cortex. In AD,
signals detected in the hippocampus are weaker than those in normals,
while signals in the cerebellum are comparable. Immunohistochemical
localization of the proteins is also primarily in ***neurons*** , and,
at least for PS-1, is reduced in AD affected areas. PS-1 is localized to
granular structures which are most abundant in cell bodies and dendrites.
The functions of the ***presenilins*** are not yet known, but
available evidence points to pyramidal ***neurons*** as the most
logical site for pathological change in AD.

L57 ANSWER 12 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:471351 BIOSIS
DN PREV199799770554
TI Effects of inducible expression on ***presenilins*** on cell proliferation and ***cell*** ***death*** .
AU Kang, David E. (1); Kammescheidt, Anja; Koo, Edward H.
CS (1) Dep. Neurosci., Univ. Calif. San Diego, La Jolla, CA 92093 USA
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 824.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1
New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

L57 ANSWER 13 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:471344 BIOSIS
DN PREV199799770547
TI Dissecting functional domains of ***presenilins*** .
AU Hong, Chang-Sook; Koo, Edward H.
CS Dep. Neurosci., Univ. Calif. San Diego, La Jolla, CA 92093 USA
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 823.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1
New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

L57 ANSWER 14 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:471341 BIOSIS
DN PREV199799770544
TI Characterization of ***presenilin*** overexpressing cerebellar ***neuronal*** cells.
AU Weggen, S.; Diehlmann, A.; Ida, N.; Czech, C.; Weidemann, A.; Masters, C.;
Wiestler, O. D.; Beyreuther, K.; Bayer, T. A.
CS Dep. Neuropathol., Univ. Bonn Med. Cent., Sigmund-Freud-Str. 25, 53105
Bonn Germany
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 822.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1
New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.
DT Conference; Abstract; Conference
LA English

L57 ANSWER 15 OF 23 MEDLINE DUPLICATE 8
AN 1998067216 MEDLINE
DN 98067216
TI Cell and molecular neurobiology of ***presenilins*** : a role for the
endoplasmic reticulum in the pathogenesis of Alzheimer's disease?.

AU Mattson M P; Guo Q
CS Sanders-Brown Research Center on Aging and Department of Anatomy and
Neurobiology, University of Kentucky, Lexington, USA..
MMattson@aging.coa.uky.edu
NC NS30583 (NINDS)
AG10836 (NIA)
AG05144 (NIA)
+
SO JOURNAL OF NEUROSCIENCE RESEARCH, (1997 Nov 15) 50 (4) 505-13. Ref: 71
Journal code: KAC. ISSN: 0360-4012.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199803
EW 19980305
AB Mutations in genes encoding ***presenilin*** -1 (PS-1) and ***presenilin*** - ***2*** (PS-2) cause many cases of autosomal
dominant inherited forms of early-onset Alzheimer's disease (AD). PSs are
expressed in ***neurons*** throughout the nervous system, with
differences in abundance among cell populations. PS-1 and PS-2 each have
six to eight transmembrane domains and are localized mainly in the
endoplasmic reticulum (ER). PSs may interact with cytoskeletal proteins
and beta-amyloid precursor protein (APP) in ways consistent with roles in
membrane trafficking and APP processing. Expression of mutant PSs in
cultured cells and transgenic mice results in increased production of an
amyloidogenic-cytotoxic form of amyloid beta-peptide (Abeta). Neural cells
expressing mutant PSs exhibit increased sensitivity to ***apoptosis***
induced by trophic factor withdrawal and Abeta. The proapoptotic action of
mutant PSs involves perturbed calcium release from ER stores and increased
levels of oxidative stress. PS mutations may also suppress
neurotransmitter synthesis in cholinergic ***neurons*** , suggesting a
role in regulation of ***neuronal*** phenotype. Homology of PSs with
the C. elegans gene sel-12 and phenotypic similarities of PS-1 and Notch
knockout mice suggest a developmental role for PSs in somitogenesis.
Collectively, the emerging data suggest intriguing roles of PSs in
neuronal plasticity and ***cell*** ***death*** and
highlight the importance of the ER as a regulatory site involved in the
pathogenesis of ***neuronal*** degeneration in AD.

L57 ANSWER 16 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:395321 BIOSIS
DN PREV199799694524
TI Superoxide free radical and intracellular calcium mediate A-beta-1-42
induced endothelial toxicity.
AU Suo, Zhiming (1); Fang, Chunhong; Crawford, Fiona; Mullan, Mike
CS (1) Roskamp Lab., Dep. Psycbiatry, 3515 E. Fletcher Ave., Univ. South
Fla., Tampa, FL 33613 USA
SO Brain Research, (1997) Vol. 762, No. 1-2, pp. 144-152.
ISSN: 0006-8993.
DT Article
LA English
AB The 39-42 amino acid residue amyloid beta peptide (A-beta), the major
protein component in senile plaques and cerebrovascular amyloidosis in the
brain in Alzheimer's disease (AD), has been shown to be neurotoxic in
vitro. Accumulating data from several areas suggest that cerebrovascular
dysfunction and damage may also play a significant role in the AD process.
For instance, we have recently demonstrated enhanced vasoconstriction and
resistance to relaxation in intact rat aorta treated with A-beta (Thomas
et al., beta-Amyloid-mediated vasoactivity and vascular endothelial
damage, Nature, 380 (1996) 168-171). Significant vessel damage occurred
after thirty minutes of exposure, but could be prevented with superoxide
dismutase. To further investigate the role of A beta toxicity on
endothelial cells, we have applied AP peptides to cultures of human aortic
endothelial cells (HAEC). Our results show that both A beta-1-42 and A
beta-25-35 are toxic to HAEC in a time- and dose-dependent manner, and
that this toxicity can be partially prevented by the calcium channel
blocker, verapamil, and the antioxidant, superoxide dismutase. The common
form of A beta, A beta-1-40, which has been shown to be neurotoxic, is
much less toxic to HAEC. AG toxicity to HAEC occurs within 30 min of
treatment with relatively lower doses than those usually observed in
primary cultured ***neurons*** and vascular smooth muscle cells. It
was recently reported that a variety of mutations in the beta-amyloid
protein precursor gene and the ***Presenilin*** -1 and -2 genes linked
to early-onset familial AD cause an increase in the plasma concentration
of A beta-1-42 in mutation carriers (Scheuner et al., Secreted amyloid
beta-protein similar to that in the senile plaques of Alzheimer's disease
is increased in vitro by the ***presenilin*** 1 and 2 and APP
mutations linked to familial Alzheimer's disease, Nature Med., 2 (1996)
864-8701. Human aortic endothelial cells are more sensitive to A beta-1-42
than A beta-1-40, via a pathway involving an excess of superoxide free
radicals and influx of extracellular calcium. Finally, we have evidence
that both apoptotic and necrotic processes are activated by the AP
peptides in these endothelial cells.

L57 ANSWER 17 OF 23 MEDLINE
AN 97134506 MEDLINE
DN 97134506
TI Dissecting how presinilins function--and malfunction [news].
AU Marx J
SO SCIENCE, (1996 Dec 13) 274 (5294) 1838-40.
Journal code: UJ7. ISSN: 0036-8075.
CY United States
DT News Announcement
LA English
FS Priority Journals; Cancer Journals
EM 199703

L57 ANSWER 18 OF 23 MEDLINE DUPLICATE 9
AN 97094374 MEDLINE
DN 97094374
TI Participation of ***presenilin*** ***2*** in ***apoptosis*** :
enhanced basal activity conferred by an Alzheimer mutation.
AU Wolozin B; Iwasaki K; Vito P; Ganjei J K; Lacan`a E; Sunderland T; Zhao B;
Kusiak J W; Wasco W; D'Adamio L
CS Unit on Alzheimer Biology, Laboratory of Clinical Science, National
Institute of Mental Health, Building 10, Room 3D41, 9000 Rockville Pike,
Bethesda, MD 20892, USA.. ldadamio@atlas.niaid.nih.gov
SO SCIENCE, (1996 Dec 6) 274 (5293) 1710-3.
Journal code: UJ7. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199703
AB Overexpression of the familial Alzheimer's disease gene

Presenilin
2 (PS2) in nerve growth factor-differentiated PC12 cells increased
apoptosis induced by trophic factor withdrawal or beta-amyloid.
Transfection of antisense PS2 conferred protection against
apoptosis induced by trophic withdrawal in nerve growth factor-differentiated or amyloid precursor protein-expressing PC12 cells.
The apoptotic ***cell*** ***death*** induced by PS2 protein was
sensitive to pertussis toxin, suggesting that heterotrimeric GTP-binding
proteins are involved. A PS2 mutation associated with familial Alzheimer's
disease was found to generate a molecule with enhanced basal apoptotic
activity. This gain of function might accelerate the process of neurodegeneration that occurs in Alzheimer's disease, leading to the earlier age of onset characteristic of familial Alzheimer's disease.

L57 ANSWER 19 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:547081 BIOSIS
DN PREV199699269437
TI Alzheimer's PS-1 L286V mutation increases ***neuronal*** vulnerability
to A-beta toxicity and trophic factor withdrawal-induced ***apoptosis***
.
AU Guo, O. (1); Sopher, B. L.; Furukawa, K.; Robinson, N.; Martin, G. M.;
Mattson, M. P.
CS (1) Sanders-Brown Res. Cent. Aging, Univ. Kentucky, Lexington, KY 40536
USA
SO Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 1664.
Meeting Info.: 26th Annual Meeting of the Society for Neuroscience
Washington, D.C., USA November 16-21, 1996
ISSN: 0190-5295.
DT Conference
LA English

L57 ANSWER 20 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:547073 BIOSIS
DN PREV199699269429
TI Genetic dissection of ***presenilin*** functions in a ***neuronal***
precursor cell line.
AU Hong, Chang-Sook; Koo, Edward H.
CS Harvard Medical Sch., Cent. Neurol. Dis., Brigham Women's Hosp., Boston,
MA 02115 USA
SO Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 1662.
Meeting Info.: 26th Annual Meeting of the Society for Neuroscience
Washington, D.C., USA November 16-21, 1996
ISSN: 0190-5295.
DT Conference
LA English

L57 ANSWER 21 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:552862 BIOSIS
DN PREV199699275218
TI Characterization and analysis of ***presenilin*** ***2*** in
mammalian cells: Effects of expression on cell viability.
AU Crowley, A. C. (1); Merriam, D. E.; Kovacs, D. M.; Kim, T.-W.; Wasco, W.
CS (1) Genetics Aging Unit, Dep. Neurology, Mass. General Hosp.-East, Boston,
MA 02129 USA
SO Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 1437.
Meeting Info.: 26th Annual Meeting of the Society for Neuroscience
Washington, D.C., USA November 16-21, 1996
ISSN: 0190-5295.
DT Conference
LA English

L57 ANSWER 22 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:552860 BIOSIS
DN PREV199699275216
TI Developmentally regulated expression of Alzheimer-related ***presenilin*** genes (PS-1 and PS-2) matches notch in mouse brain.
AU Berezovskaja, O. (1); Page, K.; Xia, M. Q.; Berezovskii, V.; Wasco, W.;
Tanzi, R.; Hyman, B. T.
CS (1) Dep. Neurol., Mass. General Hosp., Boston, MA USA
SO Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 1436.
Meeting Info.: 26th Annual Meeting of the Society for Neuroscience
Washington, D.C., USA November 16-21, 1996
ISSN: 0190-5295.
DT Conference
LA English

L57 ANSWER 23 OF 23 CAPLUS COPYRIGHT 1999 ACS
AN 1997:227701 CAPLUS
DN 126:304309
TI Alzheimer's Disease: melting pot or mosaic?
AU Blass, John P.
CS Burke Medical Research Institute, Cornell University Medical College,
White Plains, NY, 10605, USA
SO Alzheimer's Dis. Rev. [Electronic Publication] (1996), 1(1/2), 17-20
CODEN: ADREFN
URL: http://www.coa.uky.edu/ADReview/blass.htm
PB Sanders-Brown Center on Aging, University of Kentucky
DT Journal; General Review; (online computer file)
LA English
AB A brief review with 18 refs. Alzheimer's Disease (AD), like the proverbial elephant, can be described in a no. of ways, all of which are
accurate and all of which are incomplete. AD can be described, correctly,
as: a loss of synapses; a premature loss of ***neurons*** in a selectively vulnerable pattern, often assocd. with ***apoptosis*** and
other mechanisms of ***cell*** ***death*** which involve free
radicals; a disorder of free radical metab. ("oxidative stress"); a cerebrometabolic disease involving impaired glucose/energy metab.; a
cytoskeletal disease; a form of cerebral amyloidosis; a disorder of signal
transduction; a disorder of cerebral calcium homeostasis; a membrane
disorder; and a disorder of neurotransmission, with prominent impairment
of cholinergic function and more variable but typical involvement of other
neurotransmitter systems. Mol. genetic studies to date suggest that the
most important trait predisposing to the common, late onset form of AD is
possession of the 4 allele of the ApoE gene. Studies in progress suggest
the possibility that a genetic abnormality in a component of the Krebs
tricarboxylic acid cycle (the a-ketoglutarate dehydrogenase complex) is
also be important factor in the common, late onset form of AD. In the
rarer, early onset familial forms of AD (FAD), the most common genetic
abnormalities appear to be the ***presenilin*** -1 or ***presenilin*** - ***2*** -genes, which seems likely from the
predicted amino acid sequences to lead to abnormalities in signal
transduction or cellular calcium homeostasis. Abnormalities in the gene
for the amyloid precursor protein were the first mutations assocd. with
AD, but in fact have proven to be rare even in FAD. Based on currently
available data, any one of the mechanisms listed above could be proposed
to be the central step in the pathophysiol. of AD, with other mechanisms
acting through their effects on that "mainstream" abnormality. An alternative hypothesis is that a complex mosaic of abnormalities leads to
the pattern of brain scarring which characterizes AD. Different parts of

the mosaic may have or more or less important roles, depending on genetic
endowment and environmental factors. Different parts of the mosaic may
interact with each other. For instance, the abnormality in glucose/energy
metab. in AD which the authors and others have been studying may well
influence the progression of the disease by diminishing the ability of
nerve cells to adapt to challenges ("stressors") created by other
mechanisms which are part of AD. Precedents for this "mosaic hypothesis"
include other complex degenerative diseases which are better understood
than AD, such as atherosclerosis or clotting disorders.

=> d his

(FILE 'HOME' ENTERED AT 15:56:10 ON 11 APR 1999)

FILE 'MEDLINE' ENTERED AT 15:56:17 ON 11 APR 1999
L1 407 S PRESENILIN?/AB,BI
L2 0 S L1 AND ADVANCED GLYCATION END PRODUCT/AB,BI
L3 0 S L1 AND RAGE/AB,BI
L4 71 S ADVANCED GLYCATION END PRODUCT/AB,BI
L5 478 S L1 OR L4
L6 114 S L5 AND NEURON?/AB,BI
L7 111 S L1 AND NEURON?/AB,BI
L8 3 S L4 AND NEURON?/AB,BI
L9 4 S (L4)(3A)(RECEPTOR#)/AB,BI

FILE 'MEDLINE, EMBASE, BIOSIS, WPIDS, CAPLUS' ENTERED AT 16:02:33 ON 11
APR 1999
L10 0 S L1 AND L9
L11 10 S MUTANT PRESENILIN-2/AB,BI
L12 4 DUP REM L11 (6 DUPLICATES REMOVED)
E STERN DAVID/AU
L13 162 S E3
L14 0 S L13 AND PRESENILIN?/AB,BI
E YAN SHI DU/AU
L15 80 S E2-E3
L16 0 S L15 AND PRESENILIN?/AB,BI
E WOLOZIN, BENJAMIN/AU
E WOLOZIN, B/AU
E WOLOZIN B/AU
L17 201 S E3-E10
L18 23 S L17 AND PRESENILIN/AB,BI
L19 12 DUP REM L18 (11 DUPLICATES REMOVED)
E STERN D/AU
L20 527 S E3
L21 1 S L20 AND PRESENILIN/AB,BI
L22 56 S L9
L23 5 S L22 AND NEURON?/AB,BI
L24 5 DUP REM L23 (0 DUPLICATES REMOVED)
L25 1 S L9 AND GLIAL/AB,BI
L26 1 S L9 AND MICROGLIAL/AB,BI
L27 1 S L9 AND ASTROCYTE#/AB,BI
L28 18 S L9 AND ENDOTHELIAL/AB,BI
L29 15 DUP REM L28 (3 DUPLICATES REMOVED)
L30 6 S L9 AND MONONUCLEAR/AB,BI
L31 6 DUP REM L30 (0 DUPLICATES REMOVED)
L32 4 S L9 AND TUMOR#/AB,BI
L33 4 DUP REM L32 (0 DUPLICATES REMOVED)
L34 2 S L9 AND PC12/AB,BI
L35 2 DUP REM L34 (0 DUPLICATES REMOVED)
L36 88 S L1 AND PC12/AB,BI
L37 0 S L36 AND L9
L38 37 S L1 AND TUMOR#/AB,BI
L39 31 DUP REM L38 (6 DUPLICATES REMOVED)
L40 8 S L1 AND MONONUCLEAR/AB,BI
L41 2 DUP REM L40 (6 DUPLICATES REMOVED)
L42 10 S L1 AND ENDOTHELIAL/AB,BI
L43 4 DUP REM L42 (6 DUPLICATES REMOVED)
L44 61 S L1 AND ASTROCYTE#/AB,BI
L45 26 DUP REM L44 (35 DUPLICATES REMOVED)
L46 27 S L44 AND PRESENILIN-2/AB,BI
L47 13 DUP REM L46 (14 DUPLICATES REMOVED)
L48 19 S L1 AND MICROGLIA#/AB,BI
L49 7 DUP REM L48 (12 DUPLICATES REMOVED)
L50 41 S L1 AND GLIA#/AB,BI
L51 23 DUP REM L50 (18 DUPLICATES REMOVED)
L52 16 S L50 AND PRESENILIN-2/AB,BI
L53 7 DUP REM L52 (9 DUPLICATES REMOVED)
L54 500 S L1 AND NEURON?/AB,BI
L55 135 S L54 AND PRESENILIN-2/AB,BI
L56 43 S L55 AND (CELL DEATH OR APOPTOSIS)/AB,BI
L57 23 DUP REM L56 (20 DUPLICATES REMOVED)

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	ENTRY	SINCE FILE SESSION	TOTAL
FULL ESTIMATED COST		443.85	448.19

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE TOTAL	ENTRY	SESSION	
CA SUBSCRIBER PRICE		-18.21	-18.21

STN INTERNATIONAL LOGOFF AT 16:33:10 ON 11 APR 1999